Solid Tumour Section
Review

Lung: Non-small cell carcinoma

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Identity

Note
See also the overview on lung tumors.

Classification

Non-small cell carcinomas are divided into three main categories according to the predominant morphology of the tumour cells as determined by light microscopy. Although it is possible to distinguish different histological sub-groups in this way, or by using gene expression profiling, treatment is currently decided on the basis of tumour staging, age and performance status and is independent of tumour histology. In the future, this may change as new drugs are developed and as more information is gathered on the predictive power of such expression profiles.

Clinics and pathology

Pathology

Squamous cell carcinoma:
Approximately 30% of lung tumours are classified as squamous cell carcinomas (SCC). Whilst this was the most common sub-type seen in the past, the incidence of SCC appears to be decreasing relative to adenocarcinoma, probably as a consequence of historical changes in the way that cigarettes are smoked (lower tar and filter tips promoting deeper inhalation). SCC cells are large, flattened and stratified with a high cytoplasm to nucleus ratio. Key diagnostic features include the presence of intracytoplasmic keratin which may be linked to the presence of intercellular bridges and squamous pearl formation. Most SCC arise centrally within the main, lobar, segmental or subsegmental bronchi but some occur more peripherally. The tumour mass generally extends into the lumen of the airway with invasion into the underlying wall.
Adenocarcinoma:
A further 30-50% of tumours are defined as adenocarcinomas (ADC). This tumour type is the most common in non-smokers and women and it is more frequently associated with pleural effusions and distant metastases. ADC may be further sub-classified into: acinar (gland forming), papillary, bronchioalveolar (BAC), solid with mucin and mixed.
As most ADC are histologically heterogeneous, they generally fall into the mixed category. The tumours usually arise in the smaller peripheral airways (as distinct from the cartilage bearing bronchi) but they can be found more centrally. The key diagnostic features of ADC include gland formation—where the tumour cells are arranged around a central lumen—and/or mucin production. ADC is the tumour type most commonly found associated with fibrotic scars, which are thought to be caused in some way by the tumour. BAC, which represents 2-6% of total lung cancer, is distinct from other sub-types both in terms of its growth pattern, which is lepidic (typically arising beyond the terminal bronchioles, where it spreads along the alveolar septa causing minimal structural damage) and by the fact that it is non-invasive.
Large cell carcinoma:
Approximately 10% of NSCLC are defined as large cell carcinomas (LCC). This is a diagnosis of exclusion. Where a poorly differentiated tumour has none of the defining features of SCLC, SCC or ADC it may be classified as LCC: that is, where the cells of the lesion are not-columnar in shape, do not contain
adenocarcinoma. The bronchial epithelium of the larger airways is a pseudo-stratified epidermal layer. The most frequent cell types present are ciliated columnar cells, interspersed mucous-producing goblet cells and, lying closely against the basement membrane, multi-potent basal epithelial cells. The basal (or reserve) cell has a repair capacity in that it is able to differentiate, as required, into the other mature cells of the larger conducting airways. In the smaller terminal and respiratory bronchioles, basal cells are not present. The reserve cells of these epithelia are the cuboidal, non-ciliated Clara cells. It has been suggested that the multi-potent basal cell or a stem cell precursor of such cells may represent a common lung cancer progenitor.

In chronic smokers, the cells of the tracheo-bronchial tree are repeatedly exposed to a range of carcinogenic compounds. Consequently, histologically-recognisable reactive and pre-neoplastic changes can generally be seen scattered throughout the airways of long-time smokers. In situ (pre-invasive) carcinoma (CIS: full thickness cytological atypia, increased nuclear to cytoplasmic ratio) is a recognised precursor of squamous cell carcinoma. This is the end of a spectrum of pre-neoplastic transformation that ranges from squamous metaplasia (change in appearance of cuboidal cells towards squamous morphology) through mild to severe dysplasia (loss of polarity, increasing disorder) to CIS. A second pre-neoplastic state is represented by Atypical Adenomatous Hyperplasia (AAH). This is a bronchioalveolar proliferation of slightly atypical cuboidal cells that falls short of the criteria for BAC: it is a recognised precursor to adenocarcinoma.

Cytopathology

Note

Lung carcinomas represent the end-stage of the neoplastic transformation of a stem (or stem-cell like) cell that has been repeatedly exposed over many years to high levels of multiple carcinogens. It is therefore not surprising that the genetic and epigenetic lesions seen in lung cancer cells are complex. Correspondingly, frequent numerical and structural chromosomal alterations are reported in NSCLC. Whilst many changes are common, some perhaps occurring more often in one histological class over another, few if any have been shown to be exclusive to particular sub-types of disease or prognostic groupings.

At the molecular level, highly complex patterns of allelic imbalance (LOH) have been observed in primary tumours. Again, few if any of these have been strongly related to diagnosis or prognosis. No balanced chromosomal translocations have yet been associated characteristically with NSCLC.

Cytochromatics

Cytogenetics Morphological

The generally low mitotic index of lung carcinomas makes karyotypic analysis difficult. However, common numerical changes observed include the losses of chromosomes 9 and 13 and trisomy for chromosome 7. Unbalanced rearrangements have been reported to occur frequently within chromosomes 1, 3, 5, 6, 7, 8, 9, 11, 13, 14, 15, 17 and 19 and it is thought that the loss of genetic material due to such events might encompass, to some lesser extent, all chromosome arms. Arms which frequently show clear loss include; 9p, 3p, 6q, 8p, 9q, 13q, 17p, 18q, 19q, 21q, and 22q with those often associated with gains being 7p, 7q, 1q, 3q, 5p, 11q and 12q.

Cytogenetics Molecular

Comparative genomic hybridisation (CGH) has been used to extend conventional karyotypic analysis in NSCLC. Prominent imbalances seen in several studies include losses of 3p, 8p, 9p, 13q and 17p and gain of chromosome arms 1q, 3q, 5p and 8q. Regional amplification has been reported for 3q26, 8q24, 3q13, 3q28-qter, 7q11.2, 8p11-12, 12p12 and 19q13.1-13.2. Minimally localised under-represented regions include 3p14-21, 8p21-23 and 17p12-13. CGH analysis has also suggested that some alterations are more commonly seen in particular NSCLC sub-types with gain of 3q24-qter more common in SCC than ADC and gain of 1q22-32 more common in ADC than SCC.

Genes involved and proteins

Note

Consistent somatic mutation of coding sequence in primary tumours is strong evidence that a particular gene has been or is involved in the development of a neoplastic phenotype. In common with a range of tumours, particular genes are therefore clearly associated with NSCLC initiation or progression. These include TP53 (17p13.1), CDKN2A encoding p16 and p14 (9p21.3) and KRAS2 (12p12.1). Each of these genes lies within a region identified cyogenetically as implicated in NSCLC. The amplification of chromosomal regions containing genes implicated in cell growth has also been reported in primary NSCLC, albeit at a relatively low frequency. Such data are suggestive of the involvement of these sequences in neoplasia but they are weaker than direct mutational evidence given that the amplified regions generally contain a number of distinct genes, the relative contributions of each of which to the tumour phenotype is usually unknown. Genes reported as...
amplified in primary lesions include CCND1, encoding cyclin D1 (11q13.3), TP73L, encoding p63 (3q28), KRAS2 (12p12), MYC (8q24.21) and EGFR (7p11.2). A number of genes that are encoded from within chromosomal regions which show LOH or homozygous deletion in certain lesions have been identified. Such sequences may show a lack of expression in primary tumour cells compared to at least most of the cells in normal lung tissue. This lack of expression may in turn be correlated with hypermethylation of the relevant promoter sequence. Examples of such genes include RASSF1A (3p21) and CDKN2A (9p21.3). It is tempting to speculate that genes which show high levels of promoter methylation in tumour over normal tissue have been somatically inactivated by such methylation and are therefore likely to represent causally involved tumour suppressors. Whilst this may well be true in specific instances, especially where the gene in question is mutationally inactivated in a separate fraction of lesions (CDKN2), it may not be so generally, as the methylation level seen in the tumour may be completely appropriate for the cell type of origin of the particular lesion. Whilst the data suggesting the involvement of an individual gene in a tumour type might not be compelling, when pathways or control points are considered, the evidence often becomes much stronger. The best example of this is perhaps damage to the genetic system controlling progression through the G1 restriction point of the cell cycle, beyond which the cell is committed to divide. Proteins intimately involved in this key decision point, cyclin D1, p16, and pRB are frequent targets of NSCLC miss-regulation and may be involved at the earliest stages of pre-neoplastic development.

Microarray analyses: Recent microarray analyses have shown that gene expression profiling can be used to sub-divide tumours into existing histological classes. Perhaps more importantly, analyses of adenocarcinoma series have demonstrated that sub-groups of stage 1 lesions with better or worse survival can be identified from their expression patterns. Such data suggest that tumour behaviour may be, at least to some point, fixed very early in the disease process. From a different perspective, many genes have been shown to be commonly differentially expressed (over-represented) in NSCLC compared to normal lung, to some extent at least, irrespective of general histology. Such genes are potential diagnostic targets. More importantly, the study of their function, normal expression patterns and mechanisms of expression control may shed considerable light on the biology of lung cancer and the characteristics of the cell type(s) of origin. Preliminary analyses of genomics and/or proteomics highlighted sequences (S100A2, SERPINB5 encoding maspin and TP73L, encoding p63) in lung tumours and pre-neoplastic lesions supports such hypotheses and raise the possibility that some measure of tumour gene expression may result from a failure to appropriately inactivate particular sequences involved in the self-renewal phenotype of stem-cell (like) progenitors. It is anticipated that in the future, further detailed molecular investigations of gene expression in disease and normal tissues will lead to new prognostic, predictive, diagnostic, therapeutic and preventative tools.

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