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Polygenic inheritance of predisposition to lung cancer

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Summary. - Inherited predisposition to lung tumor development appears to be a complex genetic trait, in humans as well as in experimental animals. In humans, tobacco smoking represents the main risk factor for lung tumors. Familial clusterings of lung cancer cases are rare, although affected sib pairs are reported. However, several studies have reported an increased risk of lung cancer in first degree relatives of lung cancer patients, as compared with appropriate controls. Inheritence of particular alleles of genes or phenotypes for drug metabolizing enzymes are also associated with an increased lung cancer risk. In experimental models, murine inbred strains with high genetic predisposition to lung cancer are available, as well as resistant strains. A major locus affecting inherited predisposition to lung cancer in mice has been mapped on chromosome 6, near the *Kras2* gene. The locus, *pulmonary adenoma susceptibility 1* (*Pas1*) derives from the A/J strain. Additional "minor" loci have also been mapped. Dominant lung tumor resistance loci have also demonstrated in the mouse genome. Therefore, evidence for polygenic inheritance of predisposition to lung cancer is demonstrated in the mouse model, and it is strongly suggested for human lung cancer.

Key words: inbred strains, experimental models, disease susceptibility, linkage mapping.

Riassunto *(Ereditarietà poligenica della predisposizione al cancro polmonare)*. - La predisposizione ereditaria allo sviluppo dei tumori polmonari è un tratto genetico complesso, sia nell'uomo che negli animali da esperimento. Nell'uomo, il fumo di tabacco rappresenta il principale fattore di rischio per questo tumore. Aggregazioni familiari di tumore polmonare sono rare, anche se riportate. Tuttavia, diversi studi epidemiologici hanno dimostrato un aumento del rischio di tumore polmonare in parenti di primo grado dei pazienti con tumore polmonare, rispetto a controlli appropriati. Particolari polimorfismi genetici a carico di geni codificanti per enzimi coinvolti col metabolismo di sostanze esogene sono anche associati con un aumento del rischio di cancro polmonare. Nei modelli sperimentali, sono disponibili ceppi murini inbred sia suscettibili che resistenti allo sviluppo di tumore polmonare. Un locus importante per la predisposizione genetica al tumore polmonare è stato mappato sul cromosoma 6, vicino al gene *Kras2*. Tale locus, definito *"pulmonary adenoma susceptibility 1" (Pas1)* deriva dal ceppo A/J. Ulteriori loci "minori" di suscettibità sono stati localizzati su altri cromosomi. Loci che conferiscono resistenza dominante ai tumori polmonari sono stati anche identificati nel genoma di topo. Quindi, l'ereditarietà poligenica della predisposizione al cancro polmonare è stata dimostrata chiaramente nel modello sperimentale, ed è stata fortemente indicata anche nell'uomo.

Parole chiave: ceppi inbred, modelli di malattia, suscettibilità genetica, mappatura genetica.

Genetics of lung tumors in humans

Lung tumor is a relatively common type of cancer in humans. Exposure to environmental carcinogens, including tobacco smoking, represents the main risk factor for lung tumors [1]. However, not all smokers develop lung cancer, and it is possible that other risk factors, including genetic factors, are implied in the pathogenesis of lung tumors in humans. Although familial clusterings of cases are rare, several studies have considered the possible role of genetic factors in human lung cancer risk [2, 3].

The risk of lung cancer in relatives of lung cancer patients has been examined in case-control studies by comparing first-degree relatives in case families with control families. Usually, the spouses of the cases were taken as controls. Tokuhata & Lillienfeld [4] demonstrated a 2-2.5 excess risk of lung cancer in smoking relatives of cases compared with smoking relatives of controls. Lynch *et al.* [5] reported a significant increase in all cancers among the relatives of lung cancer probands. However, in the same relatives, they did not find evidence for increased lung tumor risk [5]. Ooi *et al.* [6] studied first-degree relatives of lung cancer cases and of their spouses. The case relatives had a relative risk of 2.4 for lung cancer when compared with the control relatives, after adjusting for smoking and occupational exposure. Sellers *et al.* [7] showed a relative risk of 2.5 for lung cancer among siblings of lung cancer cases when compared to siblings of the controls' spouses. By segregation analyses of the same families studied previously [6], Sellers *et al.* [8] suggested that, after tobacco exposure, the pattern of

lung cancer is best explained by Mendelian co-dominant inheritance of a single autosomal locus that influences the age at onset of lung cancer [9]. The results of their analysis indicated that: (a) genetic predisposition to lung cancer is expressed only in the presence of tobacco smoke, and therefore, lung cancer is the result of a gene-environment interaction and (b) the influence of genetic factors in lung cancer pathogenesis is much greater than previously estimated, and most lung cancers may occur among gene carriers. However, they did not test genetic models that included polygenic inheritance of the character.

Rare cases of lung cancer clustering in twins and siblings have been reported [10-13]. Three reports showed a common histotype of alveolar cell carcinoma [11, 12] or squamous cell carcinoma [10] in affected cases, whereas the other one showed different histotypes, although 3 out of 4 cases were NSCLCs [13]. Two families with a high occurrence of lung tumors, as well as of other cancers, were reported [14]. In one family, 5/10 siblings had lung tumors. In the second family, 4/8 siblings had lung cancers, which also occurred in 3/11 members of the next generation over 40 years of age. In both families different histotypes of lung cancers, mostly NSCLCs, were observed. Lung cancer was associated with smoking habits in all cases [14].

A number of case-control studies have been reported on the possible association between lung cancer risk and particular haplotypes or phenotypes of genes coding for enzymes involved with drug metabolism, including carcinogen metabolism. These studies are based on the fact that cigarette smoking is associated with an increased risk for different histological types of lung tumors, including lung adenocarcinomas [1]. Cigarettes contain a number of different chemical carcinogens that must be activated by endogenous enzymes to form reactive chemical species capable of covalently binding to DNA so as to cause mutations. Indeed, mutations of the KRAS2 gene have been identified in a high percentage of lung adenocarcinomas, and the presence of KRAS2 mutations have been associated with cigarette smoking [15-17]. Since the metabolism of chemical carcinogens involves a variety of phase I and phase II enzymes, genotypic differences at the loci coding for these enzymes may lead to differences in the endogenous activation of chemical carcinogens and consequently, to differences in lung cancer risk.

A possible association between genetic predisposition to lung cancer and the inheritance of specific alleles or phenotypes at P450 (CYP1A1, CYP2D6, CYP2E1), and glutathione S-transferase (GSTM1) loci has been reported [18-22]. However, some other studies have failed to confirm this association [23-29]. The increased risk reported in the positive studies varied from 2 to 3.

Taken together, the epidemiological studies indicate that genetic predisposition to lung cancer plays some role in the risk of lung cancer, but it is certainly not due to the Mendelian inheritance of a single gene. Rather, inherited predisposition to lung cancer appears to be a complex genetic trait, characterized by genetic heterogeneity, small effects of single genetic loci coding for metabolic enzymes, and interaction between environmental carcinogens and unknown gene(s). Complex genetic systems are very difficult to study in humans. However, if we have a good experimental model of inherited predisposition to lung cancer available, we can take advantage of this model to identify the genetic loci affecting susceptibility to lung cancer. Indeed, mouse inbred strains with high genetic predisposition to lung cancer have been selected and they may provide a tool for the dissection of the complex genetics of the disease.

Genetics of lung tumors in experimental models

Inheritance of susceptibility to lung tumors in mice was first shown by Lynch as early as 1926 [30]. Since its establishment in 1921, the inbred strain A mouse has progressively become the model for most subsequent studies on lung tumor susceptibility. In the 1930s, Strong [31] and Bittner [32, 33] reported the high spontaneous incidence of pulmonary tumors in this strain. Andervont [34] showed that virtually all young mice of this strain developed multiple lung tumors within 2 months of the subcutaneous application of dibenz[*a*,*h*]anthracene. Subsequently, Heston [35, 36] carried out detailed genetic studies by crossing the A strain with different mouse strains. As a result, he reached the following conclusions: a) lung tumor susceptibility is a partially dominant trait, since F1 animals between susceptible and resistant strains are intermediately susceptible; b) multiple genes are involved in determining lung tumor susceptibility. He was the first to suggest that this susceptibility behaves as a "quantitative character controlled by multiple factors" [35, 36]. Some studies have indicated that susceptibility to lung tumorigenesis is determined by a single gene, while other studies have suggested that multiple genes are involved. This discrepancy may be due to the different strain combinations used [32, 37-40]. The mouse inbred strains that have been identified so far as highly susceptible to lung carcinogenesis comprise the A, SWR, O20, and NGP mice [41-44].

Inbred mice represent a good model system for the identification of the number and chromosomal localisation of genetic loci predisposing lung tumor development. Indeed, linkage studies may be carried out by crossing two parental strains with large phenotype differences. The resulting F1 mice are then crossed together to obtain an F2 generation, characterised by the segregation of the phenotypic trait and of the parental alleles at any genetic locus, including loci affecting the phenotype (lung tumor susceptibility). Alternatively, F1

mice may be back-crossed to one of the parental strains or to a third strain with a recessive or null phenotype, producing a back-cross or a test-cross population, respectively. We crossed the A/J strain with the genetically resistant C3H/He strain. The resulting F2 population was treated with a single low dose of urethane, which induces many tumors in susceptible strains but very few, if any, in resistant strains [45]. The lung tumor susceptibility phenotype was evaluated quantitatively by using different parameters [45]. We typed 90 genetic markers, dispersed over all the autosomes, and mapped a "major" locus associated with lung tumor development (*Pas1*) on the distal part of mouse Chromosome 6, near the *Kras2* gene (Table 1). No other chromosomal region was linked to lung tumor susceptibility [46]. The *Pas1* locus explained up to 45% of the variance in our cross and was supported by a LOD score > 9.

We then repeated our genetic linkage study in an interspecific cross that, in addition to the A/J strain, included the *M. spretus* mice, a strain evolutionary distant from laboratory mice, that offers a great level of allelic polymorphisms [47].

In the interspecific cross we confirmed the location of *Pas1* locus on the distal region of chromosome 6, close to *Kras2* [48]. In the same cross, we obtained evidence of the existence, on chromosome 11, of a lung tumor resistance locus derived from *M. spretus* (Table 1). This locus strongly decreased the expressivity of the *Pas1* allele, but it did not affect lung tumor susceptibility in mice that do not carry the susceptible *Pas1* allele [49].

Data from Festing *et al.* [50] showed that at least four genes are associated with susceptibility to lung carcinogenesis in (A/J x C57BL/6)F2 cross. They confirmed the location near the *Kras2* locus on chromosome 6 of the "major" *Pas1* locus, which accounted for 60% of the total variation in their cross. In addition, they found three "minor" loci associated with lung tumor development on chromosomes 9, 17 (in the *H2* complex), and 19 (Table 1). They found no significant associations with 32 other loci located on all autosomes [50]. Devereux *et al.* [51] confirmed the mapping of *Pas1* and of the "minor" locus on chromosome 19 (Table 1).

Several studies have indicated that the *H2* complex, or genes close to *H2* on chromosome 17, affect lung tumorigenesis in mice [52-54]. Two recent reports, one in (A/J x C57BL/6)F2 mice, and the other on two *H2* congenic strains confirmed the location of a putative "minor" lung tumor susceptibility locus in the *H2* region [50, 55]. However, we have not found associations between loci close to *H2* and lung tumor susceptibility in either AC3F2 or ASB crosses [46, 48] (data not shown). The discrepancy may be due to the different crosses and experimental schedules.

Collectively, the genetic linkage studies in mice indicate that the *Pas1* locus on mouse chromosome 6 plays a major role in the inherited predisposition to lung tumors in mice. However, additional unlinked susceptibility and resistance alleles have been detected. Therefore, polygenic inheritance determines predisposition to lung cancer in mice.

Comparative aspects

Inherited predisposition to lung tumorigenesis in mice is of great interest as a model system for understanding pathogenetic mechanisms. At present, it is not clear if these studies have applications for humans. Therefore, it is important to establish whether the mouse lung tumors represent the experimental counterpart of a human lung tumor histotype. Once the correspondence between mouse lung tumors and a particular human lung tumor histotype is established, it will be possible to transfer the results obtained in the experimental models to the human situation.

A large portion of the mouse genome shows regions of homology and conserved syntenies with the human genome, and comparative genetic maps between mice

Table 1. - Murine loci containing putative lung tumor susceptibility/resistance genes, as detected by genetic linkage studies

Chromosome	Locus name	Cross	Variance explained (%)	Ref.
6	*Pas1*	(A/J x C3H/He)F2	≅ 40	[46]
		(A/J x C57BL/6)F2	≅ 60	[50]
		(A/J x C57BL/6) x C57BL/6J	≅ 16	[51]
		(A/J x *M. spretus*) x C57BL/6J	≅ 40	[48]
9	*Pas4*	(A/J x C57BL/6)F2	≅ 4	[50]
11	*Par1*	(A/J x *M. spretus*) x C57BL/6J	≅ 15	[49]
17	*Pas2*	(A/J x C57BL/6)F2	≅ 7	[50]
19	*Pas3*	(A/J x C57BL/6)F2	≅ 2	[50]
		(A/J x C57BL/6) x C57BL/6J	≅ 3	[51]

and humans have been used to predict the location of human and murine disease genes on the basis of their mapping in other species [56]. The mapping of the genes responsible for genetic susceptibility and resistance to lung carcinogenesis in the mouse chromosomes, and the subsequent analysis of homology between mice and humans on the chromosomal regions containing putative tumor susceptibility and resistance gene(s), would suggest that we should test genetic markers localised in the corresponding human chromosomal region for possible linkage with the risk of lung tumor in humans. The identification of the chromosomal localisation of loci predisposing lung tumor development could be the first step towards the cloning and identification of these genes. Once the murine genes affecting lung tumor susceptibility are identified and cloned, it will be possible to test their human homologues for the presence of mutations in human lung tumors and in the germ-line of patients affected with a lung tumor.

Mouse lung tumors represent the experimental model for human lung adenocarcinomas. Indeed, mouse lung tumors and human lung adenocarcinomas show similar histology, similar pattern of KRAS2 gene mutations, similar alterations in gene expression, and loss of heterozygosity (LOH) at homologous chromosomal regions [57, 58]. Although a complete overlap in the characteristics of mouse lung tumors and human lung adenocarcinomas does not occur, the common features outweigh the differences.

Conclusions and perspectives

Several studies have indicated the possible important role of genetic factors in human lung cancer risk. However, familial lung cancer is rare and the lack of familial clusters of lung cancer patients indicates the low penetrance or the polygenic nature of inherited predisposition to lung cancer. Therefore, the identification and cloning of single genetic elements affecting predisposition to lung cancer would be very difficult in humans.

The murine strains predisposed to lung tumor development may provide a unique experimental system for the analysis of the genetics of these tumors. A "major" genetic locus affecting susceptibility to the development of lung tumors (*Pas1*) has been mapped on the mouse genome by genetic linkage analysis experiments. Other "minor" susceptibility loci, and loci affecting dominant resistance to lung carcinogenesis are presently being mapped. Finally, the results of genetic linkage studies could provide a clear picture of the number and chromosomal location of loci affecting lung tumorigenesis in the experimental system. This will be the first step toward the cloning of lung tumor susceptibility and resistance genes.

Although the positional cloning of the *Pas1* locus affecting lung tumor development is difficult, due to the relatively large regions of linkage (5-10 cM, that may contain hundreds of genes), this goal is possible. Indeed, the obese (*ob*) gene has recently been cloned based on results of genetic linkage experiments [59]. New developments in the methodologies for the positional cloning of genes may allow us to clone the *Pas1* gene and other "minor" loci affecting lung tumor development in the near future.

Once the genes responsible for susceptibility to lung tumorigenesis in mice are cloned, it is relatively easy to find the human homologues and to look for the presence of mutations and/or allelic variations in cancer patients and in the general population. The identification of subjects at genetic risk for lung cancer may be useful to implement cancer prevention strategies in people at genetic risk.

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