Angiogenesis and the Multistage Development of Lung Cancers

Adi F. Gazdar and John D. Minna

The Hamon Center for Therapeutic Oncology Research and Departments of Pathology, Internal Medicine, and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390

As with other epithelial tumors, lung cancers develop after a series of morphological and molecular changes. The molecular alterations precede histopathological changes and commence in histologically normal epithelium (1, 2). In the larger bronchi, the smoking-associated morphological changes can be followed endoscopically, and they include hyperplasia, squamous metaplasia, squamous dysplasia (of varying degrees), and CIS. Many of these changes cannot be recognized by routine endoscopy and require the specialized technique of fluorescence bronchoscopy for their identification (3). Molecular studies and clinical observations suggest that hyperplasia and metaplasia may be reactive changes rather than true preneoplasia. These lesions frequently regress after smoking cessation and have molecular changes similar to those of histologically normal epithelium, whereas foci of dysplasia and CIS have more advanced molecular changes (4) and may persist for many years after smoking cessation (5). In this issue of Clinical Cancer Research, Keith et al. (6) describe a newly recognized putative preneoplastic lesion, ASD, in the bronchi of subjects at increased risk for lung cancer (heavily exposed current and former smokers).

The concept that angiogenesis was essential for the development and behavior of solid tumors was popularized by Folkman in 1971 (7). An increasing number of angiogenic factors have been identified, and tumor cells may release several of these factors (8–10). Angiogenic factors affect vasculature formation, growth patterns, and vascular permeability; modulate host response; and influence tumor invasion, metastasis, and prognosis. Among the most important angiogenic cytokines are the VEGFs. They and their receptors are prime regulators of both physiological and pathological angiogenesis (10). The secretion of angiogenic substances by tumors and their precursor cells has been referred to as an angiogenic switch (8), and it is induced by several factors including hypoxia and alterations in dominant and recessive oncogenes including p53 and ras (11, 12). The angiogenic factors complex with high-affinity receptors on endothelial cells, stimulating angiogenesis. The demonstration of VEGF-receptor complexes (13) on the surface of tumor endothelial cells is one method to document the angiogenic switch. Because neoangiogenesis is essential for sustained tumor growth, inhibitors of angiogenesis are currently being explored as therapeutic agents (14). Whereas the association of angiogenesis with invasive and metastatic tumors is well documented, some evidence indicates that angiogenesis commences during multistage carcinogenesis (8, 15).

The crucial role of angiogenesis in lung cancer development is documented by the presence of more than 100 relevant citations. Increased vessel density may be an important prognostic factor in resected non-small cell lung cancer (16), and it is present in dysplastic lesions (17), indicating that angiogenesis is a relatively early event during cancer pathogenesis. Angiogenesis is an integral part of the ASD lesions described by Keith et al. (6). Whereas histological accounts of similar lesions have been reported for over 50 years, this is the first detailed description of multiple cases. ASDs are small lesions in which capillary loops project into histologically abnormal bronchial epithelium. The resultant architectural rearrangement forms micropapillary lesions in which capillary loops are covered by attenuated strips of multilayered epithelium that is usually squamous and dysplastic in appearance.

ASD lesions were identified in 54 of 158 (34%) smokers without cancer and in 6 of 10 (60%) patients with squamous carcinoma. In one case, an ASD lesion was contiguous with the accompanying invasive carcinoma, suggesting that the ASD may have been a direct precursor lesion. ASD lesions were not present in 16 never smokers, indicating that ASD lesions are smoking related. In some subjects, ASDs were present at multiple sites in both lungs. As with other bronchial lesions, most ASDs could not be recognized by routine white light bronchoscopy but required fluorescence examination for identification. In our experience (in collaboration with Dr. Stephen Lam (British Columbia Cancer Agency, Vancouver, British Columbia, Canada)), approximately 40% of all dysplastic bronchial lesions demonstrate the characteristic morphological changes of ASD. Compared with normal epithelium, ASD lesions (and non-ASD dysplasias) had an increased proliferative fraction and an elevated microvessel density in the adjacent subepithelial tissues. A more convincing method to document the onset of the angiogenic switch in ASD lesions would be to demonstrate the presence of VEGF in the dysplastic cells or the appearance of VEGF-receptor complexes in the subepithelial vessels (13). Allelic losses at the short arm of chromosome 3 (an early and frequent event in lung cancer pathogenesis) were present in over half of the ASD lesions. p53 mutations (genetic alterations occurring later in lung cancer pathogenesis) were absent, except in a single unusual case of a smoker having a specific mutation at multifocal sites. As with the overall pattern of bronchial dysplasia (5), ASDs showed gender bias and were more frequent in male smokers.

However, ASDs may present diagnostic and clinical problems. The attenuated epithelium overlying the capillary loops makes it difficult to identify the specific grade of dysplasia. In
addition, as noted by Keith et al. (6) and by us, micropapillary lesions may be associated with metaplasia or hyperplasia instead of dysplasia. Is a name containing the word dysplasia suitable for lesions without dysplasia? Do all of these variations have the same prognostic implications? We would have preferred a term such as angiogenic micropapillary lesion (with hyperplasia, metaplasia, or dysplasia). Do ASDs truly demonstrate the angiogenic switch, and if so, what is the mechanism? Hypoxia is unlikely to be responsible for the switch in a relatively thin surface epithelium. Although ASDs lacked p53 mutations, the relationship between oncogene activation and ASD should be further explored. Are ASDs that lack dysplasia less likely to progress to cancer? It should also be kept in mind that squamous dysplasia and CIS are only associated with squamous cell carcinomas. What about the other 70–75% of lung cancers in which the sequence of preneoplastic changes is less well defined (adenocarcinomas) or unknown (small cell and large cell carcinomas)? There is some evidence that peripheral lung lesions termed AAH may be precursor lesions of adenocarcinomas (18). With the advent of screening methods for lung cancer using low-radiation dose computed tomography (19), AAH lesions will be recognized more frequently. Do some of these AAH lesions demonstrate the angiogenic switch, and, if so, what is its clinical significance?

How can we interpret these very interesting observations? They suggest (as do earlier reports) that the angiogenic switch occurs relatively early during lung cancer pathogenesis. It may be possible to divide dysplastic lesions into those with or without the angiogenic switch. However, it remains to be determined whether subjects with ASD lesions are at greater risk for progression than smokers with conventional dysplastic lesions. If so, antiangiogenic therapies may be used for both cancer prevention and treatment.

Acknowledgments

We thank Dr. Phillip Thorpe for many helpful suggestions.

References

Clinical Cancer Research

Angiogenesis and the Multistage Development of Lung Cancers

Adi F. Gazdar and John D. Minna


Updated version Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/6/5/1611

Cited articles This article cites 18 articles, 6 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/6/5/1611.full.html#ref-list-1

Citing articles This article has been cited by 6 HighWire-hosted articles. Access the articles at:
/content/6/5/1611.full.html#related-urls

E-mail alerts Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.