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Oncogenic tyrosine kinases

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Tyrosine kinases (TKs) and related molecules comprise over 100 different genes. Approximately two-thirds represent receptor TKs, the other third being non receptor TKs. TKs regulate important cellular signalling, from the transduction of extracellular signals to the regulation of key biological processes such as cell proliferation and apoptosis [1, 2].

TKs can turn themselves into the engine of malignant cell transformation. In this review, seven TKs with oncogenic activity are described. Their relationship to cancer varies in the different genes analyzed, and in the different experimental models proposed and discussed. Each chapter describes a single TK, and follows a schema like the one outlined here below:

- a description of the normal counterpart of the reported oncogenic TK, and of its normal functions
- the type of cancers related to this particular TK
- what is known about the cause/effect relationship between the described TK and the generation of a certain tumor in humans
- whether this TK is structurally altered or overexpressed in neoplastic cells, and what is known about the molecular process by which such an alteration is formed
- the signal transduction pathways through which the described TK exerts its oncogenic activity
- what is the likely position of the described TK in the process of neoplastic transformation of involved cancer(s), and whether it represents an early or late event
- whether specific drugs are available

As the reader will find in the review, the seven selected TKs show different models and different degrees of relationship with cancer and leukemia development. They range from cases with a known, clear and causal relationship to examples in which such a relationship is more circumstantial. This latter point (relationship to transformation) constitutes one of the pivotal issues discussed here.

This review does not pretend to be exhaustive; it does not include important TKs, such as for example the receptor for epithelial growth factor (EGFR).

Although EGFR is widely expressed in normal and neoplastic epithelial cells, no strong indication of structural alteration of this molecule in cancer has been available up to now. Not surprisingly, the clinical activity of EGFR inhibitors has been quite modest. However, important clinical responses were observed in 5–10% of treated patients.

Two independent groups of investigators recently reported that almost all responding patients bear heterozygous activating mutations of EGFR, while patients not responding to treatment present a wild-type sequence [3, 4]. Lynch, Paez and colleagues found missense or deletion mutations inside the catalytic domain of EGFR in almost all patients affected by non-small cell lung cancer (NSCLC) who developed objective and durable resonses to gefitinib, an EGFR inhibitor. Mutations were more common in patients with adenocarcinoma or bronchoalveolar carcinoma, in women, in nonsmokers and in patients of Japanese origin. Tumors from NSCLC patients not treated with gefitinib also showed the presence of EGFR alterations in variable precentages (from 2 to 32%, depending on patient selection).

Interestingly, some mutations were present inside the same domain (the p loop) where mutations develop in chronic myeloid leukemia patients who developed resistance to imatinib, a Bcr/Abl inhibitor. However, in the case of NSCLC the mutations actually increased the sensitivity to gefitinib, and also increased the activity of the enzyme following EGF stimulation.

These findings will allow us to target EGFR only in those patients in which the gene represents a meaningful target for therapy. It not yet known, however, whether EGFR mutations represent early or late events in the transformation process.

The recent identification of activating mutations in the catalytic domain of EGFR in patients affected by lung

cancer and their strong association with clinical responses to an EGFR inhibitor are a further testimony to the importance of defining the molecular pathways that lead to a certain cancer, and to the therapeutic relevance of such knowledge.

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2 Noble M., Endicott J. A. and Johnson L. N. (2004) Protein kinase inhibitors: insights into drug design from structure. Science **303:** 1800–1805

3 Paez G., Jaenne P. A., Lee J. C., Tracy S., Greulich H., Gabiel S. et al. (2004) EGFR mutations in lung cancer: correlation with clinical responses to Gefitinib therapy. Science **304:** 1458–1461

4 Lynch T. J., Bell D. W., Sordella R., Gurubhagavatula S., Okimoto R. A., Brannigan B. W. (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small cell lung cancer to gefitinib. NEJM, **350:** 2129–2139