## Molecular pathways in human cancers

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**Introduction** Bioinformatic analysis of genetic data on human tumors is challenged to predict the spontaneous course and the response to available therapies (summarized as ‚prognosis'), in order to facilitate optimized ‚individualized' treatment of each patient. These analyses must take into account technical limits of the methodology used to acquire the data as well as biological restraints on their significance. Both differ between tumor types.
**Material and Methods** The molecular pathways active in two prototypic tumor types, chronic myeloid leukemia (CML) and urothelial cancer (UC), are delineated and the complications for bioinformatic approaches to prognosis arising from the type of genetic alterations in each tumor type are discussed.
**Results** The clinical course of CML [1,2] can be divided in three phases, chronic phase, accelerated stage, and the fatal blast crisis. CML is characterized by the specific chromosomal alteration, t(9;22), a translocation between chromosomes 9 and 22. This alteration allows definitive diagnosis of the disease and is intially accompanied by few other genetic and epigenetic changes. The number of chromosomal alterations, point mutations, and epigenetic alterations, such as promoter hypermethylation, increases through the accelerated phase towards blast crisis. Response to treatment with cytostatic drugs and interferons is highly variable, but diminishes with tumor progression. A novel antitumor drug, imatinib, is targeted against the fusion protein that is produced as a consequence of the diagnostic t(9;22) translocation. This drug is highly efficacious in most chronic phase patients, but tumors in the progression stages typically escape by various mechanisms that include mutation or amplication of the target gene or loss of dependence on the fusion protein for growth. UC [3,4] occurs in two quite distinct types. Papillary UC is characterized by few chromosomal alterations and in many cases point mutations in a specific growth factor receptor. This subtype is much less lethal than invasive UC which is characterized by the presence of multiple chromosomal alterations and increasing promoter hypermethylation. These alterations disturb the regulation of several regulatory systems, including regularly cell cycle regulation by the RB1 network and control of genomic stability by the TP53 network. However, the mechanisms of and consequentially the extent of deregulation of either network differ between individual tumors.
**Discussion** At least in its early, chronic phase, the prognosis of CML can be reliably predicted because a limited number of chromosomal alterations is present and one of them is essential for tumor growth. While an increase in chromosomal alterations as such is indicative of progression, the differences in spontaneous course and response to therapy become more difficult to predict, most likely because the tumor cell population develops genomic instability that generates subclones with varying potential to spread and to respond to therapy. In UC, the papillary and invasive subtypes can be quite well distinguished by the extent of chromosomal and epigenetic instability. However, while the extent of genetic and epigenetic instability is well correlated with UC progression, its prognostic value within the subset of invasive cancers is limited. This problem arises because of the heterogeneity in the mechanisms that lead to disturbance of crucial regulatory systems and of the variety of alterations that take place in tumors with chromosomal and epigenetic instability.

### Literature

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