1. **Descrivere la cascata di segnale cellulare attivata dalla proteina chinasi MKK3 e sue funzioni nel sostenere l'aggressività tumorale.**

2. **Descrivere cosa è il Riposizionamento Farmacologico e sue potenziali applicazioni nelle patologie oncologiche.**

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Review

Genome-guided discovery of cancer therapeutic targets

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SUMMARY

The success of precision oncology—which aims to match the right therapies to the right patients based on molecular status—is predicated on a robust pipeline of molecular targets against which therapies can be developed. Recent advances in genomics and functional genetics have enabled the unbiased discovery of novel molecular targets at scale. We summarize the promise and challenges in integrating genomic and functional genetic landscapes of cancer to establish the next generation of cancer targets.

INTRODUCTION

The promise of precision medicine lies in linking drugs to specific molecular alterations in patients, thereby affording patients the therapies from which they are most likely to benefit. In oncology, successful application of the precision medicine paradigm typically requires (1) a drug that can target a gene product essential to cancer cells and (2) a molecular feature or features that can identify in which patient's tumor that gene is essential ("biomarker"). In the past two decades, rapid advances in the molecular characterization of cancer have ushered in multiple successful drug-biomarker pairs to the clinic. Still, only a minority of genetic alterations in tumor cells are currently amenable to precision medicine approaches. In this review, we discuss the potential for unbiased genomic and functional approaches to expand the list of cancer targets that can be pursued in molecularly defined patient subpopulations.

GENOMIC DISCOVERY OF CANCER GENES

Foundational discoveries establishing cancer as a genetic disease

Over a century ago, Theodor Boveri proposed a genetic basis for cancer through his prescient connection between the origin of malignant tumors and abnormalities in sea urchin development that were observed when embryos inherited an abnormal chromosome complement.[1] This conceptual advance forms the basis for our current understanding of cancer as a genetic disease, with two main classes of cancer genes: oncogenes (which become somatically activated in cancer and stimulate cell growth) and tumor suppressors (which normally repress cell growth and become somatically inactivated in cancer).[2]

In the pregenomics era, several complementary techniques were used to identify germline and somatic genetic changes associated with cancer development.[3] These included (1) cytogenetics and chromosome banding (e.g., used to identify the 9;22 Philadelphia chromosome translocation in chronic myelogenous leukemia[4,5]; (2) genetic linkage analysis (e.g., used to localize and clone the *RB* tumor-suppressor gene associated with familial retinoblastoma and the *APC* tumor-suppressor gene associated with familial adenomatous polyposis[6–8]; (3) genome-wide loss-of-heterozygosity (LOH) mapping using restriction fragment length polymorphisms (RFLPs), microsatellite markers, or single-nucleotide polymorphisms (SNPs) (used to identify multiple tumor-suppressor genes including *CDKN2A* on chromosome 9p and *SMAD4* on chromosome 18q[9–11]); and (4) comparative genome hybridization (CGH) (used to identify numerous candidate loci for oncogenes and tumor suppressors).[12]

This genetic mapping work occurred roughly contemporaneously with a series of experimental studies that established a functional link between genetic alterations and cancer development. In the 1970s, *c-src* was identified as a cellular proto-oncogene that was acquired by, and mutated in, the oncogenic Rous sarcoma virus[13,14]—the first demonstration that genetic alterations in cellular genes could drive cancer. Soon thereafter, it was shown that DNA prepared from carcinogen-transformed rat cell lines or human cancer cell lines could transform NIH3T3 mouse fibroblasts.[15] Hybridization analysis revealed that the causative oncogene, *RAS*, was homologous to the transforming genes of the Harvey (ras^H) and Kirsten sarcoma (ras^K) viruses and that it arose via genetic alteration of a cellular proto-oncogene.[16–19] Conversely, transfection of wild-type *p53*, a tumor-suppressor gene, into colorectal carcinoma cells harboring biallelic inactivation of this gene was shown to suppress cancer cell growth.[20]

Functional studies in animal models subsequently demonstrated the role of these and other initially discovered cancer genes in cancer development.[21–23]