VIEWPOINT

162 Separating the Wheat from the Chaff: Identifying SNPs Associated With Disease

Non-synonymous single nucleotide polymorphisms (SNPs) that result in amino acid substitutions may have no appreciable effect on protein function, but those that involve critical residues may cause or contribute to disease. Large-scale gene sequencing studies have revealed a daunting number of non-synonymous SNPs with unknown functional consequences. Both predictive techniques and functional assays can aid in the identification of disease-relevant SNPs, as illustrated by two recent reports. An insightful comparison of known disease-causing vs uncharacterized SNPs in protein kinases sheds new light on regions of the catalytic core. The observed prevalence of disease-causing SNPs in substrate binding and regulatory regions—but paucity thereof in residues directly involved in the catalytic reaction—will likely extend to other enzymes as well. A clever functional bioassay using mouse ES cells distinguishes neutral from deleterious mutations in the breast and ovarian cancer-related BRCA2 gene, which may aid in the interpretation of patient BRCA2 screening data.

Joan L. Cmarik

REVIEWS

165 GPCR Signals and Integrin Backtalk

G protein–coupled receptors are a mainstay of pharmacology and remain the most targeted molecules in clinical history. Typically, soluble ligands reach GPCRs and initiate cascades of protein–protein and enzymic interactions that affect cytoplasmic and nuclear metabolism. Migration, survival, and proliferation are some of the basic cell functions that are regulated by means of GPCR signaling. Increasingly, the extracellular matrix has become appreciated for its active role in nuancing these functions and integrating cell–cell communication essential to tissue physiology. The matricellular protein CYR61/CCN1 has recently been shown to be expressed in response to canonical GPCR-activated signaling pathways. Furthermore, secreted CYR61/CCN1 interacts with integrins and other elements of the ECM and thereby adds a novel dynamic to GPCR and ECM signaling. Recognition of CYR61/CCN1 as a regulator of crosstalk between intra- and extracellular signaling pathways also opens up new opportunities for experimental therapeutics.

Colin T. Walsh, Dwayne Stupack, and Joan Heller Brown

174 Using Phytochemicals to Fight Cancer

Recent research into the origins of cancers suggests the cancer stem cell is the source of both initial tumor formation and eventual patient relapse. Cancer stem cells have the ability to self-renew as well as to give rise to the multiple cell types present within the tumor. Investigations into the biology of cancer stem cells have revealed that they express large amounts of drug pumps and have active self-renewal and anti-apoptosis pathways that involve the participation of well-characterized signaling proteins and transcription factors. These characteristics may render cancer stem cells susceptible to pharmacological intervention. Intriguingly, certain plant-derived compounds interfere with the capacity of cancer stem cells to pump out cytotoxic agents, differentiate, or resist programmed cell death. Indeed, many phytochemicals are currently under evaluation in clinical trials and may prove themselves as valuable adjuncts to front-line cancer therapies.

Brian T. Kawasaki, Elaine M. Hurt, Tashan Mistree, and William L. Farrar