

Faculty Research Interests: Cancer Track of the Biomolecular Pharmacology Training Program

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Research Interests: Dr. Cohen's laboratory is addressing the molecular basis of renal cancer, renal cystic disease and renal development and offers special expertise in gene expression mechanisms, signal transduction, protein-protein interactions, transcription factors, and renal epithelial cell biology. The laboratory has identified the first member of new protein family, the Jade family of proteins, on the basis of its interaction with the von Hippel-Lindau tumor suppressor pVHL. pVHL protein is a key component of the cellular oxygen-sensing system. VHL is also the major renal cancer gene in adults. Jade-1 is a novel, growth suppressive plant homeodomain transcription factor that is the first protein found to be stabilized by pVHL. Jade-1 is also a ubiquitin ligase and key component of histone acetylation complexes. Interestingly, Jade-1 is stabilized by VHL protein in a manner that correlates with risk of renal manifestations in von Hippel-Lindau disease, which includes a cystic renal disease phenotype. A wider role for Jade-1 in renal cyst formation was therefore sought. Jade-1 is regulated by the product of the major gene for autosomal dominant polycystic kidney disease (ADPKD), polycystin-1, in a manner that is also disease relevant and physiologic. Importantly, Jade-1 serves as a critical ubiquitin ligase for the oncoprotein beta-catenin, which also plays key roles in renal cancer, renal cyst formation and renal development. This work identifies the canonical Wnt signaling pathway and beta-catenin as potential pharmacologic targets in these disorders, and this possibility will be explored. By controlling gene transcription and beta-catenin ubiquitination, Jade-1 and related family members are likely to be particularly important in many contexts.

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Research Interests: Our laboratory studies the roles of proto-oncogene proteins in the signal transduction pathways that control proliferation and survival of mammalian cells. Current research is focused on the mechanisms by which the phosphatidylinositol 3-kinase (PI 3-kinase)/Akt signaling pathway, which is one of the major pathways targeted by oncogenic mutations in human cancers, regulates cell survival by suppressing apoptosis. The targets of PI 3-kinase/Akt signaling include the Bcl-2 family member Bad, a variety of transcription factors, and the protein kinase GSK-3. Substrates of GSK-3 also include a variety of transcription factors, as well as the translation initiation factor eIF2B. It thus appears that PI 3-kinase/Akt/GSK3 signaling regulates gene expression at both the levels of transcription and translation. At the translational level, we have found that inhibition of translation resulting from phosphorylation of eIF2B plays an important role in apoptosis, at least in part due to turnover of the Bcl-2 family protein Mcl-1, whose rapid degradation couples global translational regulation to cell survival.

Our studies of transcriptional regulation have used global gene expression profiling to identify genes that are regulated by PI 3-kinase/Akt/GSK-3 signaling. We have combined these results with computational prediction of transcription factor binding sites to identify transcription factors that are targeted by the PI 3-kinase/Akt/GSK3 pathway. These computational predictions coupled with experimental verification have identified FOXO, NFkB, and CREB as key targets of PI 3-kinase signaling. We are extending these studies with the goal of elucidating the

transcriptional regulatory network that coordinates PI 3-kinase-regulated gene expression in mammalian cells.

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Research Interests: The canonical Wnt pathway is essential for embryonic development and it is dysregulated in cancers. Our long-term goal is to characterize the mechanism of Wnt signaling to understand the role of the Wnt pathway in development and cancer. We are focusing our studies on the function, regulation and mechanism of action of two components of the Wnt pathway: the serine-threonine kinases CK2 and GSK3beta. We are using *Xenopus* frog embryos and cell culture to understand the molecular mechanism of action of CK2 and GSK3beta in Wnt signaling. Understanding how the Wnt pathway is normally activated is a prerequisite to understand its dysregulation displayed in cancers. Utilizing *Xenopus* embryos, we have shown that CK2 is sufficient and necessary for canonical Wnt signaling. Ongoing studies focus in determining the mechanism of regulation of Wnt signaling by CK2, and in the development and testing of novel CK2 inhibitors *in vivo* in *Xenopus* and *in vitro* in breast and colon tumor cell lines.

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Research Interests: Multicellular organisms consist of various highly specialized cells that are known to express different sets of specific proteins and perform diverse functions. How do cells with identical genetic information feature a variety of phenotypes? An important mechanism accounting for such differences operates on an epigenetic level and utilizes chromatin structure. It has become clear that proper packaging of DNA strands is not the only function of chromatin. By virtue of dynamic post-translational modifications and protein-protein interactions, chromatin can regulate DNA metabolism and transcription. The proper functioning of this chromatin-mediated signal transduction network is required for DNA maintenance and integrity, whereas defects are known to result in inappropriate cell division, DNA damage and instability leading to various diseases.

Our long-term goal is to determine mechanisms and roles of chromatin and factor modifications in regulation of DNA replication and transcription. We have characterized the novel PHD zinc finger protein PHF17/JADE1 and reported for the first time that JADE1 is a key regulatory protein and is required for activation of HBO1 complex, which is a HAT Binding Origin Replication Complex1. The HAT activity of HBO1 is thought to be important the cell cycle progression. We also demonstrated that PHD zinc fingers of JADE1 are specifically required for HBO1 to acetylate histone H4 within a nucleosome. We proposed a hypothesis that unlike chromo-, bromo-, or SET-domains, the PHD zinc fingers of JADE1 target a HAT complex to the nucleosomal histones regardless of their modification state. This finding might unravel a novel mechanism to target nuclear protein complexes to chromatin by a subset of PHD zinc fingers. We are investigating a potential role of JADE1 PHD zinc fingers in cell cycle-related activities of HBO1 complex. Several HAT complexes have been linked to diseases, including cancers.

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Research Interests: Our major research focus is on the use cancer genomics, employing primarily breast, colon and lung cancers as model systems, to shed light on genomic instability, genetic and epigenetic aberrations and metastasis of cancer. Furthermore, we are also interested in unravelling the role of the epigenome in the pathogenesis of major psychiatric disorders such as schizophrenia and bipolar disorder. Our pioneering studies showed that *SMAD4* is the major target tumor suppressor gene localized to the minimally lost region on chromosome 18q. Currently, we are testing the hypothesis that the direct/indirect inactivation of Smad4 is a major switch for benign to metastatic form of colon cancer. TGF-beta levels are increased in advanced breast cancers and believed to induce epithelial mesenchymal transition (EMT), a critical process during cancer progression. We exploited a model system and found that TGF-beta regulates promoter DNA methylation of genes during the acquisition of the EMT phenotype. We are extending these studies to examine other modes of epigenetic regulation and the molecular basis of these effects. We have also proposed a simplified scheme to explain the complexity in cancer progression as alternations that accrue in a series of a cascade of sub-network modules and elicited as events in a multi-modular molecular network (MMM_N) of cancer progression.