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“All of the experiments in this publication were performed in our lab in Hansen 105 by Libby Porter, an exceptional graduate student,” comments Dr. Dykhuizen. “The groundwork for these studies were established by Dev Chowdhury and others in our previous PLoS One publication from last year.”

Kidney cancer is the 8th most common cancer in the United States, and clear cell renal cell carcinoma (ccRCC) is the most common and deadly type. If it spreads from the kidney, there are few available treatment options and patients frequently die in a manner of months. The Dykhuizen lab studies Polybromo1 (PBRM1), a gene which is mutated in 40% of ccRCC patients. In patients, mutations in PBRM1 often lead to a loss of PBRM1 protein; however, missense mutations (mutations that change a single amino acid) in PBRM1 have been identified. These mutations tend to cluster in bromodomains, which are regions of the protein that bind specific signals on nucleosomes, the proteins that package DNA. In their previous work, they found that PBRM1 was important for regulating genes involved in preventing cancer. In this study, they found that four of the six bromodomains are required for PBRM1 tumor suppressor function with the degree of importance correlating strongly to the rate of missense mutations found in patients. Furthermore, they identified the second bromodomain as the most critical for PBRM1 function and identified its binding partner on nucleosomes to be histone H3 acetylated at lysine 14 (H3K14Ac).

“Using a combination of genetic and biochemical approaches, we determined the importance of bromodomain 2 for PBRM1 function in kidney cancer, which allowed us to dissect out H3K14Ac as critically important for PBRM1 targeting,” she says. “This mark is induced during metabolic stress conditions found in the tumor, and is necessary for PBRM1 to upregulate genes that halt cancer growth. This is really exciting breakthrough for us as it provides us with a model for how to decipher the context specific roles for PBRM1 in development, cancer, and homeostasis, and to use that information to specifically tailor therapies for kidney cancer patients with PBRM1 mutations.”