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Bad Timing: Early Molecular Events Impact Tumor Fate

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Research conducted under the supervision of Richard Halberg, Ph.D
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Chelsie Kohns Sievers's Dissertation Abstract

“Bad Timing: Early Molecular Events Impact Tumor Fate”

Colorectal cancer encompasses multiple subtypes of tumors that are defined by their molecular and histological features. Historically, these features were thought to be attained by the sequential acquisition of driver mutations over time. However, this model of tumor evolution fails to account for the variability in polyp growth behavior and the ubiquitous presence of intratumoral heterogeneity. These observations have led to new models of tumor evolution in which numerous molecular changes occur simultaneously during punctuation events. We sought to test this new conceptual framework by characterizing how and when crucial molecular characteristics are acquired and their impact on tumor evolution. Microsatellite instability (MSI) is common in many familial and sporadic colorectal cancers. We developed a more sensitive method for detecting MSI in tumors to determine when it is acquired. MSI can occur early in the development of adenomas from Lynch patients or it can occur later in the development of tumors with a serrated morphology. The early diagnosis of Lynch Syndrome could be of immense clinical benefit as each patient has, on average, three afflicted relatives, many of whom go undiagnosed until they present with a cancer. Our analysis of intestinal tumors also revealed that other molecular events occur earlier than predicted. Colorectal tumors can have different fates: growth, stasis, or regression. The comparison of gene expression in growing tumors versus static tumors from mice revealed a gene signature that could distinguish between these types. The transcriptional changes were evident as soon as tumors were detectable. Similarly, in human colorectal tumors we found that subclones carrying pathogenic mutations arose when the tumors were quite small. Furthermore, we demonstrate that many of these subclonal mutations result from a very early punctuation event. Thus, our findings support the notion that early punctuation events can affect tumor fate. The finding of critical molecular events occurring very early on during tumorigenesis support the notion that some tumors might be “born to be bad.” These novel insights may lead to more efficient screening recommendations, novel screening modalities, and improved treatment options for patients.