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When protein stability drives tumor progression

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In oncology, including immune-oncology, research often focuses either on identifying successive molecular abnormalities associated with tumor development, which may serve as potential therapeutic targets, or on defining broader regulatory mechanisms that give these changes biological meaning [1, 2]. The article by Qin *et al*. belongs to the latter category. In this issue of the *Central European Journal of Immunology* (CEJI), the authors describe RAB40C as a functionally relevant driver of prostate adenocarcinoma progression and place it within a mechanistic axis linking ubiquitin-dependent protein turnover, SNX9 stability, and Hippo pathway output [3]. Starting with weighted gene co-expression network analysis and progressing through a series of *in vitro* validation experiments, they show that RAB40C is overexpressed in prostate adenocarcinoma, supports proliferative and invasive behavior, promotes SNX9 degradation *via* the ubiquitin-proteasome system, and is associated with altered expression of Hippo pathway target proteins, including CTGF and CYR61 [3]. The study is therefore notable not only for nominating a candidate biomarker, but also for proposing a coherent molecular framework that integrates proteostatic control with oncogenic signaling [3].

This is precisely the type of work that deserves attention, and was therefore selected as an Editor's Pick. Prostate adenocarcinoma is a biologically heterogeneous disease in which clinically useful stratification still lags behind molecular complexity. While androgen receptor signaling continues to dominate therapeutic thinking, it has become increasingly clear that progression, invasion, and treatment resistance are also shaped by broader signaling architectures, including mechanoresponsive, trafficking-associated, and post-translational regulatory systems. Qin *et al*. enter this space by focusing on RAB40C, a Rab family member whose biological relevance extends beyond vesicular trafficking toward Cullin-RING ligase-associated ubiquitin signaling [3].

Over the last few years, CEJI has increasingly featured studies in which tumor behavior is interpreted through the lens of regulatory circuitry rather than descriptive oncology alone. A 2023 CEJI study classified bladder cancer according to Notch pathway activity and linked that classification to immune infiltration patterns, emphasizing that signaling states can structure the tumor ecosystem [4]. In 2024, CEJI published work showing that STK11 mutation in lung adenocarcinoma affects tumor proliferation through $CD4^+$ T-cell activity, thereby connecting genotype, tumor fitness, and immune function [5]. In 2025, the journal further highlighted mechanistic tumor immunobiology by demonstrating that ANKRD22-driven M2 macrophage polarization facilitates angiogenesis in lung adenocarcinoma and by presenting a pan-cancer analysis of PRC1 in relation to prognosis and immunotherapy response [6]. Taken together, these studies reveal a clear editorial pattern: CEJI has become increasingly interested in how intracellular signaling, epigenetic regulation, and protein networks shape not only tumor growth, but also tumor-immune and tumor-stromal behavior. The RAB40C-SNX9-Hippo study belongs squarely within that developing identity.

The broader scientific context makes these findings more significant. In recent cancer research, the Hippo-YAP/TAZ axis has increasingly been recognized as a central regulatory hub linking cell-intrinsic oncogenic programs with tissue architecture, stromal signaling, and immune regulation [7]. Recent discoveries across human cancers have shown that alterations in Hippo pathway genes are both frequent and mechanistically diverse, reinforcing the view that Hippo dysregulation is not a uniform event but rather a biologically heterogeneous process. At the same time, growing evidence indicates that YAP/TAZ activity extends well beyond tumor cell proliferation, intersecting with stromal remodeling, macrophage-associated tumor-promoting programs, and broader features of the tumor microenvironment. This evolving understanding has further established Hippo pathway effectors as important determinants of fibroblast state, immune suppression, extracellular matrix remodeling, and therapeutic responsive-

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ness [8]. Within this broader framework, the study by Qin *et al.* suggests that Hippo pathway output in prostate adenocarcinoma may be regulated upstream by a protein-stability circuit involving RAB40C and SNX9 [3]. This is a mechanistic proposition with implications that may extend beyond prostate cancer alone. Importantly, the paper also intersects with another major trend in contemporary tumor biology: the centrality of proteostasis and post-translational control. Cancer cells do not simply overexpress oncogenic programs; they continuously sculpt signaling competence through protein degradation, trafficking, and context-dependent stabilization.

For an immunology journal, the relevance of this study is not incidental. The paper is not an immune phenotyping study, nor does it directly interrogate leukocyte behavior in the prostate tumor microenvironment. Yet its significance for immunology lies in the pathways it touches. Hippo signaling is now understood to influence cytokine landscapes, stromal activation states, immune exclusion, macrophage polarization, and the broader architecture of tumor-host interaction. A molecular axis that alters Hippo pathway targets in tumor cells may ultimately shape the conditions under which antitumor immunity either proceeds or fails. In that sense, the study offers an important upstream mechanism that future work can extend into the immune microenvironment. For these reasons, the article by Qin *et al.* merits selection as an Editor's Pick. It exemplifies a direction that is increasingly important for both oncology and immunology: understanding how malignant behavior emerges from the intersection of pathway logic, protein stability, and microenvironmentally relevant signaling.

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