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Ezrin and its emerging role in tumor progression: Response

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The recent Letter to the Editor entitled “Ezrin and its emerging role in tumor progression”, Shailendra Kapoor points out that ezrin expression may be causally important to the development, metastases, and virulence of many human cancers. While comparing human cancer to hypothermic organ preservation injury mechanisms may sound disjointed, the parallelisms are actually strong and reciprocal. In these two cases, the same molecular mechanisms (stress response signaling through ezrin phosphorylation) represent opposite sides of the same coin. Our hypotheses has always been that recalibration of stress response signaling in normal cells, tissues, and organs increases the tolerance of these cells to the stresses of hypothermic preservation injury, which remain an important strategy in improving cold preservation of donor organs. Activation of Rho, Rac, and Akt kinases modify ezrin phosphorylation at key control points [1], which enhance molecular binding configurations necessary for membrane protection and suppress mitochondrial apoptosis pathways necessary for survival. These attributes are salutary in preventing injury in cold stored organs and their inactivation causally contributes to preservation injury. Conversely, activation of ezrin protects cells from preservation injury by increasing tolerance to membrane and mitochondrial injury [2,3]. Activation of these same ezrin pathways in normal cells, however, may causally contribute to malignant phenotypes such as motility and adhesion (metastases), and anti-apoptotic growth responses (tumor development). Therefore, one strategy in combating hypothermic preservation injury has been to understand molecular signaling in cancer biology because activation of some of these same pathways in organs harvested for transplantation will afford the same pro-survival signaling needed to induce tolerance to preservation stress. It’s all about context. In one case ezrin activation causes disease and in the other it causes stress protection and organ preservation. Understanding when and how to turn these pathways on and off is a key in managing both conditions.

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