437

Novel Targeting of Semaphorin 7a-Mediated Survival Signaling in ER+ Breast Cancer to Mitigate Therapy Resistance

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OBJECTIVES/GOALS: Estrogen receptor-positive (ER+) breast cancers (BC) comprise >70% of all BC and cause the most BC-related deaths in women worldwide. Despite available therapies against ER+ BC, recurrence often arises due to development of endocrine therapy resistance. Thus, our goal is to identify novel biomarkers that could serve as therapeutic targets for ER+ BC. METHODS/STUDY POPULATION: We have identified a neuroimmune molecule, Semaphorin 7a (SEMA7A), as a potential biomarker for endocrine therapy resistance, relapse, and poor survival in ER+ BC patients. SEMA7A promotes tumor growth, angiogenesis, epithelial-to-mesenchymal transition, metastasis, and endocrine therapy resistance in our pre-clinical models. Specifically, using in vivo models we have shown that SEMA7A+ MCF7 tumors result in lung metastases that do not respond to fulvestrant, in part via downregulation of ER, posing the need to identify novel, druggable targets for SEMA7A+ ER+ BC patients. SEMA7A is a membrane-bound protein that can inhibit tumor cell death via integrin-mediated PI3K/Akt pro-survival signaling. Thus, we hypothesized that SEMA7A+ ER+ BC may be sensitive to PI3K inhibition in combination with fulvestrant. RESULTS/ANTICIPATED RESULTS: Our preliminary studies confirmed that high SEMA7A expression associates with increased phospho-Akt levels and decreased apoptosis of tumor cells in forced suspension conditions. We also observed that human MCF7 ER+ SEMA7A overexpressing (OE) cells are sensitive to the PI3K (P110ï ¡ï€©ï € inhibitor, Alpelisib. Also, the combination of Alpelisib with fulvestrant inhibited tumor cell viability in MCF7 cells, which was further enhanced in the SEMA7A OE counterparts. The combination also decreased proliferation and tumor sphere formation. There are currently no therapies that directly target SEMA7A, and here I propose an innovative hypothesis that PI3K inhibition will block SEMA7A signaling. DISCUSSION/SIGNIFICANCE: The role of SEMA7A has been studied in several cancer types, but its function in ER+ BC remains less well understood. In future studies, we will explore the mechanisms by which SEMA7A signals in the cell and to promote tumor cell survival. Delineating these mechanisms will help optimize treatment combinations to improve BC patient survival.

438

Platelets, Inflammation and Thrombosis in Chronic Kidney Disease

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OBJECTIVES/GOALS: Platelets reside at the nexus of thrombosis and inflammation which make them an ideal target of investigation to understand mechanisms underlying chronic kidney disease (CKD)-related inflammatory and thrombotic dysregulation. Our objective is to determine whether a pro-inflammatory state in CKD is exacerbated by platelets. METHODS/STUDY POPULATION: Aim 1 will investigate effects of engineered reduction in the interaction of platelets with leukocytes [by disruption of one of the platelet surface receptor (GPIb-IX)] in the development of CKD in murine models. Aim 2 will investigate effects of platelet inhibitors on the development of CKD in murine models. RESULTS/ANTICIPATED RESULTS: We anticipate that the proposed studies in Aim 1 will demonstrate reduction in the interaction of platelets with leukocytes results in exacerbation of kidney injury upon CKD induction with cisplatin. We also anticipate that inhibition of platelets in Aim 2 with P2Y12 receptor inhibitors results in reduction in kidney injury upon CKD induction with cisplatin. DISCUSSION/SIGNIFICANCE: Upon successful completion of the proposed studies, we shall be able to better describe the role of platelets as modulators of inflammation in CKD. This will be a significant stride towards understanding the pathophysiology of a pro-inflammatory state in CKD and how platelets exacerbate inflammation and thrombosis in this population.

439

Research Dynamics within a New Multi-Institutional Cross-Disciplinary Translational Team (MCTT): A Formative Study

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OBJECTIVES/GOALS: This report evaluates participants'experiences from three universities who assembled a complex grant proposal related to research on post-acute sequala of COVID-19 (PASC), also called long COVID. Activities reviewed ranged from the assembly of the team to responses to reviews by the National Center for Advancing Translational Sciences (NCATS). METHODS/STUDY POPULATION: Data were collected by means of semi-structured interviews, conducted and recorded on Zoom, with a sample of 15 scientists and staff both during proposal assembly and following proposal review. The sample comprised 40% of the total team equally selected from the 3 universities, The interview protocol was reviewed by the IRB at UTMB and the interviews were recorded on Zoom, and analyzed by means of the constant comparative strategy in the grounded theory method of qualitative research. Given the relatively small number of interviews in this project, we paid special attention to preserving the confidentiality of respondents. Only the verbal tracks of the interviews were professionally transcribed. Respondents were asked to suggest changes for future inter-organizational proposals. RESULTS/ANTICIPATED RESULTS: FIRST INTERVIEWS *LEADERSHIP: The scope of leadership opportunities was expanded as sub-teams in specific areas such as community engagement were formed. *TEAM: Each university's community engagement team specializes in a different ethnic clientele, precluding a singular statement for the proposal. SECOND INTERVIEWS *LEADERSHIP: Staff members noted that the team concept too easily evolved into a bureaucratic format, resulting in less negotiation and more direction. *ASSEMBLY TASKS: The Writing Team turned out to be one of the most critical staff teams. *COMMUNICATION: The behavioral scientists in community engagement do not necessarily share paradigms (e.g., public health, psychology, and social work). They had difficulty generating productive communication and a unified statement for the proposal. DISCUSSION/SIGNIFICANCE: The scientists, as a group, suggested that future proposals should focus on one general topic, such as the microbiome, as opposed to attempting to integrate widely divergent interests. The scientists as a group should decide a priori whether to treat innovative ideas such as machine learning science as a science or a service.

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