



The biology of stress in cancer: Applying the biobehavioral framework to adolescent and young adult oncology research



Mallory R. Taylor^{a,b,*}, Jennifer M. Knight^c, Abby R. Rosenberg^{a,b}

^a University of Washington School of Medicine, Department of Pediatrics, Division of Hematology, Oncology, Seattle, WA, USA

^b Palliative Care and Resilience Lab, Center for Clinical and Translational Research, Seattle Children's Research Institute, Seattle, WA, USA

^c Departments of Psychiatry, Medicine, and Microbiology & Immunology, Medical College of Wisconsin, Milwaukee, WI, USA

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ABSTRACT

The stress response influences the development and trajectory of cancer through a host of complex neuroimmune mechanisms. Basic, translational, and clinical research has elucidated these biobehavioral connections and offers a new paradigm for scientific investigation and patient care. Using a biobehavioral approach could offer new diagnostic and therapeutic opportunities in oncology, and this approach will be particularly impactful for adolescent and young adult (AYA) patients with cancer. To date, nearly all biobehavioral oncology research has been done in the adult population. And yet, AYAs have traditionally poorer mental health and cancer-related outcomes, and thus represent a population that could benefit from parallel psychosocial and biomedical intervention. Future biobehavioral work in oncology should focus on the AYA population, integrating new cancer therapies and technology into the next generation of research.

1. Introduction

Stress physiology associated with psychosocial risk factors directly influences the development of cancer and subsequent disease trajectory (Antoni et al., 2006; Lutgendorf et al., 2010). These psychosocial risk factors can include affective state, but also extend beyond emotions to include social and environmental circumstances. For example, anxiety, depression, and lower socioeconomic status (SES) are associated with poorer cancer and hematopoietic cell transplant (HCT)-related outcomes including disease progression, graft-versus-host disease (GVHD), and survival (Stommel et al., 2002; El-Jawahri et al., 2017; Baker et al., 2009). Lower patient-reported resilience is associated with more severe GVHD and permanent disability following HCT (Rosenberg et al., 2015a). In contrast, advantageous psychosocial conditions have been associated with protective effects, including lower risk of relapse and cancer-related mortality (Andersen et al., 2008).

Biobehavioral models offer plausible explanations for how these relationships emerge in the context of cancer, and there are exciting opportunities to utilize this psychoneuroimmunology (PNI) framework in research and clinical care (Andersen et al., 1994; Knight et al., 2013). To date, much of the foundational PNI work in cancer has been carried out in the adult population, leaving an opportunity to learn more about the biopsychosocial landscape of adolescents and young adults (AYAs) with

malignancy. By leveraging the translational PNI approach, we can apply the familiar paradigm of targeted therapies for cancer to the psychosocial care of patients and families. Here, we review some of the formative basic and clinical science research in biobehavioral oncology, discuss applications in the understudied AYA population, and offer opportunities for future exploration in the field.

2. Stress, resilience, and cancer

2.1. Basic science discovery

The neuroimmune axis encompasses the integrated phenomena of subjective experience and immune system function. These connections between mental state and disease have natural implications in cancer, where extremes of psychosocial distress and immune system dysregulation often coincide. The stress response, through neuroimmune and endocrine pathways, can activate molecular signaling profiles that regulate tumor development, growth, and metastasis (Antoni et al., 2006; Lutgendorf et al., 2009; Cole et al., 2015). The sympathetic nervous system (SNS), which mediates the fight-or-flight stress response through β -adrenergic signaling, appears to be a key driver of many of these biobehavioral processes. For example, laboratory models have shown that β -adrenergic activation regulates many oncogenic processes including

* Corresponding author. Seattle Children's Research Institute, 1920 Terry Ave, MS Cure 4, Seattle, WA, 98101, USA.

E-mail address: Molly.taylor@seattlechildrens.org (M.R. Taylor).

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DNA repair, angiogenesis, inflammation, and immune cell mobility (Cole and Sood, 2012; Thaker et al., 2006; Hara et al., 2011). SNS signaling localized to the bone marrow, a critical site for metastatic tumor infiltration as well as stem cell transplant, influences the hematopoietic milieu through regulation of stem cell migration and proliferation (Katayama et al., 2006; Lucas and Frenette, 2008). Likewise, β -adrenergic signaling induces pro-metastatic gene expression signatures in orthotopic mouse models of solid tumors (Sloan et al., 2010; Kim-Fuchs et al., 2014). *In vivo* data also supports the concept that interruption of this adrenergic communication may abrogate these effects – β -adrenergic antagonism blocks stress-induced tumor progression in experimental models of carcinoma, melanoma, and leukemia (Cole and Sood, 2012).

In conjunction with the SNS, the hypothalamic-pituitary-adrenal (HPA) axis orchestrates the other arm of the stress response, with direct influence on downstream pathways instrumental to immune system function and cancer biology (Reiche et al., 2004). The hypothalamus responds to ‘stress signals’ by secreting corticotropin-releasing factor, which causes the pituitary to release adrenocorticotrophic hormone (ACTH), culminating in glucocorticoid secretion from the adrenal cortex. Glucocorticoids have well-documented immunosuppressive and immunomodulatory effects, and they may also help create biologic environments that are advantageous to cancer cells. In laboratory models of epithelial tumors, glucocorticoids have been shown to inhibit cancer cell apoptosis, antagonize cytotoxic effects of chemotherapy, and activate pro-metastatic pathways (Volden and Conzen, 2013).

Preclinical data supports a bi-directional relationship between the immune system and psychosocial experience. In other words, not only can stress physiology lead to immune dysregulation, but immune system activity may influence the development of certain behaviors or psychosocial states. For example, individual differences in interleukin 6 (IL-6) levels from stimulated leukocytes predict the later development of a stress-susceptible (versus resilient) behavioral phenotype in mice (Hodes et al., 2014). Further, hematopoietic stem cells transplanted from these stress-susceptible mice into control mice resulted in an increase in social avoidant behavior. One hypothesized mechanism for how peripheral inflammation may influence mood involves reduced integrity of the blood brain barrier and subsequent infiltration of immune cells into the brain parenchyma. Mice exposed to chronic stress show a loss of tight junction proteins and abnormal neurovascular morphology, with subsequent IL-6 passage into the brain and development of depression behaviors (Menard et al., 2017).

2.2. Translation to human subjects

These pivotal discoveries in the laboratory facilitate a mechanistic understanding of the biobehavioral pathways influencing clinical cancer biology, while complementary epidemiologic studies seek to define how these pathways impact outcomes for patients. Operating from this translational framework, we are developing a growing understanding of how the psychoneuroimmune axis contributes to a person’s risk for cancer development, progression, relapse, and likelihood for cure.

As described above, one important focus of basic PNI research in cancer is the myriad of effects exerted by the SNS and β -adrenergic signaling. This translational paradigm has been most convincingly illustrated by antagonism of the β -adrenergic pathway in patients with cancer. In a large observational study using national cancer registry data, women taking the nonselective β -blocker propranolol were significantly less likely to present with advanced stage breast cancer and had lower breast cancer-specific mortality compared to matched non-users (Barron et al., 2011). Prospective experimental studies of β -adrenergic antagonism have also shown promise. For example, a randomized placebo-controlled trial of perioperative β -blockade in patients with breast cancer resulted in improved metastatic biomarkers in the treatment arm (Shaashua et al., 2017). Similarly, in a randomized trial of propranolol in HCT recipients, inhibition of β -adrenergic signaling was associated with improved molecular profiles in patients with multiple myeloma (Knight et al., 2018).

One indicator of SNS status and β -adrenergic activity is heart rate variability (HRV), the physiologic fluctuation between successive heartbeats. HRV has been associated with both mental and physical health outcomes in epidemiologic studies (de Castilho et al., 2017; Tsuji et al., 1996; O’Neal et al., 2016; Koenig et al., 2016). In adult patients with cancer, decreased HRV has been associated with disease progression and poorer survival (Kloter et al., 2018; Guo et al., 2015), as well as late effects such as cancer-related fatigue and chronic pain (Crosswell et al., 2014; Appelhans and Luecken, 2008). In a study of 38 pediatric oncology patients, HRV predicted the development of organ dysfunction in the inpatient setting (Mayampurath et al., 2018). HRV is modifiable with training (i.e. stress-reduction techniques and exercise) or pharmacologic intervention (i.e. β -blockade) (Sandrone et al., 1994). Thus, HRV is an important indicator of both psychological and physical health with diagnostic and therapeutic implications in patients with cancer. Our team is exploring the use of HRV as a stress biomarker in AYAs with cancer, with early data suggesting this is a feasible and acceptable approach in this population (Taylor, 2021).

A key downstream effect of the stress-induced β -adrenergic pathway involves alteration in inflammatory gene expression profiles. One such profile is called the conserved transcriptional response to adversity (CTRA), which involves up-regulation of pro-inflammatory genes and down-regulation of Type I interferon genes (Cole, 2019). Importantly, CTRA biology has been associated with adverse clinical outcomes in adult oncology. In a randomized trial testing a cognitive behavioral stress management intervention in patients with breast cancer, (median age 50 years), blood samples were collected for CTRA gene expression at 6- and 12-months following surgery. Greater increase in CTRA expression over time predicted shorter disease-free survival in these patients (Antoni et al., 2016). In the adult HCT population, pre-transplant blood samples analyzed for CTRA predicted later cancer relapse and disease-free survival in two recent studies (Knight et al., 2016, 2019). Modification of CTRA biology can be accomplished through behavioral or pharmacologic intervention (Knight et al., 2018; Antoni et al., 2012). For example, β -adrenergic antagonism can reduce the CTRA profile among HCT recipients (Knight et al., 2018). Examining molecular correlates of inflammation is of particular importance in cancer, as we know that this process represents an common pathway between the malignancy (and its sequelae) and psychosocial phenomena like depressive symptoms and stress.

Taken together, the complex interplay of emotions, environment, behaviors and the immune system has important implications for cancer research and clinical practice. Bridging the laboratory and epidemiologic study of biobehavioral paradigms could offer new diagnostic and therapeutic opportunities in oncology; however, nearly all PNI-related cancer research has been conducted in older adults. This leaves a gap in our understanding of the biopsychosocial landscape in younger, more developmentally vulnerable patients with cancer.

3. AYA oncology

The relationship between psychosocial state and biology may be especially important in AYAs with cancer. AYAs, which include patients who are diagnosed between the ages of 15–39, have significantly poorer mental health, and have had less improvement in survival outcomes in the past four decades compared to older or younger patients with cancer (Kazak et al., 2004, 2010; Bleyer et al., 2006a, 2006b). Reasons for these disparities include: (a) the unique psychosocial needs of AYAs - the burdens of cancer add to the developmental stressors of identity-development, emerging autonomy, and establishing educational/vocational goals (Richardson et al., 1999; Zembrack and Isaacson, 2012); and, (b) the unique biology of AYA cancers (Tricoli et al., 2011). Unfortunately, AYAs are an understudied group in oncology more generally, with even fewer AYA-specific biobehavioral investigations. This gap is in part due to the challenging nature of conducting clinical research in this population: there are fewer patients, which often restricts

the number and types of studies that can produce meaningful clinical outcome data. Additionally, AYAs have the lowest rate of clinical trial participation across all age groups, with estimates between 2 and 10% of eligible patients (Bleyer et al., 2018).

Despite these inherent challenges, there are numerous reasons to believe that a biobehavioral approach to AYA oncology research will be a high yield endeavor. As a group with comparatively inferior cancer-related outcomes combined with a high incidence of psychosocial adversity, there is an immense opportunity to understand any interdependence between the two. This understanding could produce novel diagnostic and therapeutic targets in a population where a meaningful improvement in outcomes is both possible and urgently needed. Recent studies testing a resilience intervention (Promoting Resilience in Stress Management [PRISM]) in AYAs with cancer reported strong enrollment rates ranging from 68 to 78% of those approached (Rosenberg et al., 2015b, 2018). This suggests that compared to traditional clinical trials in oncology, AYAs may be more likely to participate in psychosocial supportive care research, which would naturally facilitate parallel biomarker data collection (e.g. blood samples, imaging, or other objective physiologic measures). Additionally, teenagers and young adults are pervasive users of technology, including smart phones and wearable devices. This comfort with digital health platforms lends itself to physiologic and biometric data gathering, which could easily be incorporated into biobehavioral AYA studies.

4. Future directions

The field of PNI offers an exciting opportunity to unite biologic and behavioral sciences in cancer research and clinical care, especially in AYA oncology (Fig. 1). The past two decades have seen an exponential growth of biobehavioral research in cancer, and this trend is likely to continue in the decades to come. To ensure sustained growth, there are some key areas to focus on moving forward.

The cellular and molecular processes by which the neuroimmune axis influences cancer biology and behavior are particularly relevant in the era of immunotherapy. Manipulation of the immune system through cytokine therapy (or blockade), immune checkpoint inhibitors, or chimeric antigen receptor (CAR) T-cells is a growing therapeutic strategy

in pediatric oncology. For example, the immune checkpoint inhibitors pembrolizumab and nivolumab are currently being tested in clinical trials for Hodgkin Lymphoma (SWOG's S1826 and the Children's Oncology Group's (COG) AHOD1822), a common AYA diagnosis. The bi-specific T-cell engager (BiTE) Blinatumomab is included in upfront therapy on the open COG trial for B-cell acute lymphoblastic leukemia and lymphoma, AALL1731. Additionally, the availability of an FDA-approved commercial pediatric CAR T-cell product (Kymriah, Novartis) and expansion of pediatric CAR T-cell trials for solid tumors (NCT03638167, NCT03618381, NCT02311621) mean more AYA patients are likely to receive these therapies in the coming years.

While harnessing the power of the immune system has shown promise in the treatment of malignancy, the neuroimmune-mediated psychosocial impacts of these interventions are largely unknown. Recent work in adult cancer patients who received CAR T cell therapy suggests that immune-mediated neurotoxicity during treatment may increase the risk of later neuropsychiatric sequelae (Ruark et al., 2020). Conversely, stress-induced HPA axis dysregulation may increase endogenous glucocorticoid release, which could blunt the intended cancer-directed immune response. The magnitude and scope of these effects may be even more pronounced in AYAs who are receiving these immunotherapies during a time of critical psychosocial development, an area that requires dedicated exploration.

As mentioned above, digital health technology offers a novel strategy for biobehavioral research and may be especially applicable in the AYA population. Wearable devices can capture valuable physiologic data such as HRV and blood pressure, and advances in biosensor technology now allow for the measurement of inflammatory cytokines and cortisol with a superficial patch on the skin (Munje et al., 2017). These approaches are often scalable and convenient; qualities that are appealing for research in patients with serious illness such as cancer, where participant burden is of particular concern. Since AYAs are native technology users, it would be relatively easy to incorporate wearables and other digital health data collection devices into future studies.

Additionally, biomarker discovery and categorization are instrumental to much of the ongoing translational biobehavioral research. This is expressly true in cancer, where disease- and treatment-related effects may confound traditional PNI analyses. Thus, it is critical to utilize strict

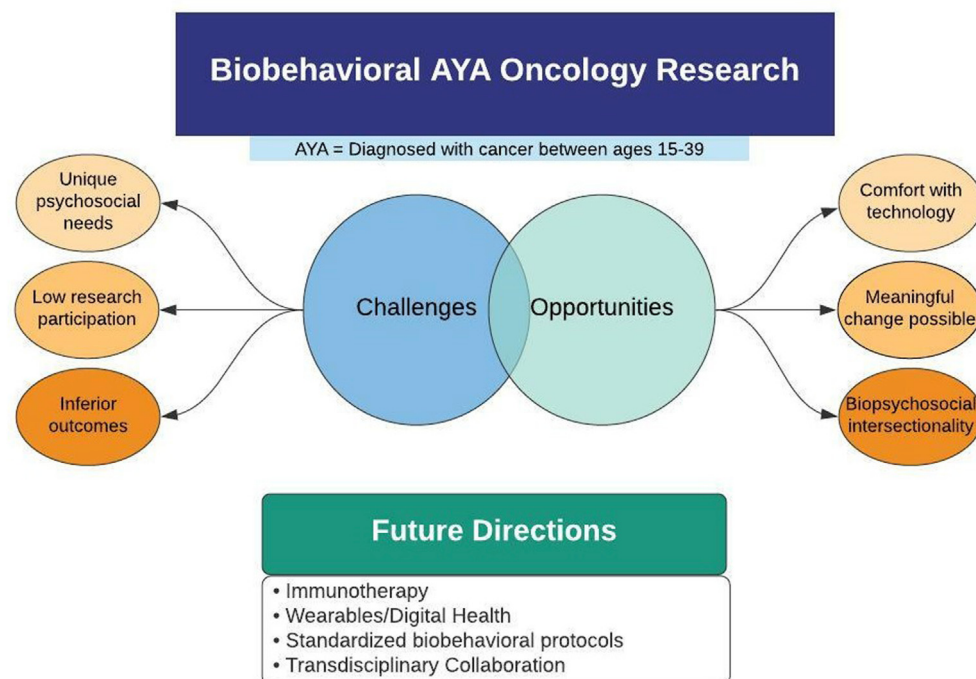


Fig. 1. Summary of biobehavioral oncology research in AYAs.

protocols when available for biomarker collection, measurement, analysis, and validation (A-H and F.a.Biomark, 2016; Shaffer and Ginsberg, 2017). In many cases, however, limited sample size, foundational data, or funding restricts the high level of interrogation that is required. Similarly, consensus guidelines for the sound conduct of PNI-based research in the context of cancer are needed. As a step in this direction, the Biobehavioral Research Special Interest Group of the American Society for Transplantation and Cellular Therapy has recently compiled an expert review in biobehavioral research and HCT (Kelly et al., 2021). We hope this review will serve as an update and guide for future investigation in this area.

Finally, rigorous PNI research in cancer requires a truly interdisciplinary approach. It is rare for an individual researcher to have overlapping training in advanced basic laboratory and behavioral science methodologies, and so we must prioritize close partnership among investigators with needed expertise. In biobehavioral AYA research, this could include stakeholders from immunology, genomics, pediatric oncology and transplant, psychology/psycho-oncology, social work, biostatistics, epidemiology, adolescent medicine, spiritual care, along with patients and caregivers, among others. Collaboration among these traditionally disparate fields is now essential to move this important work forward.

5. Conclusion

The complex interplay between the immune system and behavior has clear implications for oncology research and clinical care. In AYAs with cancer, this relationship may be particularly important, and a biobehavioral framework could offer novel therapeutic interventions for this vulnerable population. The changing landscape of cancer therapy and technology provides a unique opportunity to grow our understanding of psychoneuroimmune mechanisms in cancer. Collaborative efforts among researchers will be crucial as we embark on this next phase of discovery.

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Declaration of competing interest

None.

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Dr. Mallory Taylor grew up in rural Lockwood, Missouri. After completing her undergraduate degrees in Psychology and Microbiology at the University of Arizona, she moved to Santa Barbara, California to work for a local nonprofit organization and coach volleyball. She then moved to the east coast for her medical training at Dartmouth Medical School in Hanover, New Hampshire. She completed her Pediatrics internship at the University of Chicago and her Pediatrics residency at Seattle Children's Hospital. Dr. Taylor then moved to the small town of Kenai, Alaska to work as a general pediatrician before returning to Seattle to complete her fellowship in Pediatric Hematology/Oncology and a master's degree in Health Services from the University of Washington. She is now a junior faculty member in the Hematology/Oncology Division at Seattle Children's Hospital, primarily seeing patients with solid tumor malignancies. She is a post-doctoral investigator in the Palliative Care and Resilience Research Program at the Seattle Children's Research Institute. Her research interest is in biobehavioral pediatric oncology, seeking to understand the biologic underpinnings of stress and resilience in children and AYAs with cancer. Outside of her academic and clinical life, she enjoys exploring the beautiful pacific northwest with her husband, Dave, and daughter, Elliott.