Psychoneuroimmunology: Can psychological stress affect the initiation and progression of cancer?

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Introduction

Psychoneuroimmunology is the study of the interactions between psychological processes and the endocrine, nervous and immune systems. Communication between these three systems occurs through chemical messengers secreted by nerve cells, endocrine organs and immune cells, and psychological stressors can disrupt these networks resulting in immune related disorders such as cancer. We are constantly exposed to psychological stressors, so determining whether they can affect cancer onset and progression is of paramount importance in a society where cancer deaths increase every year.

Table 1. Types and examples of psychological stressors

Major life events	Daily stressors	Ambient stressors
Marriage/Divorce Loss of employment Death of a loved one	Meeting deadlines Making important decisions Money problems	Noise Crowding Pollution Traffic

Objectives

- Collecting bibliographic data about the psychological stress pathways that induce physiological changes
- Determining if psychological stress, through these changes, can promote cancer onset and progression
- Proposing new cancer therapeutic approaches based on the stress response
- Outlining future directions concerning psychoneuroimmunology and cancer

Stress response

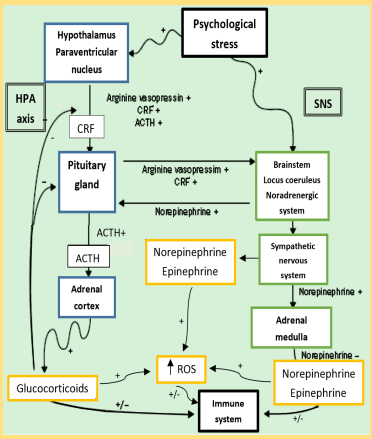


Figure 1. The stress response. Adapted from [1]

Stress results in release of **glucocorticoids** by the hypothalamic-pituitary-adrenal (HPA) axis, and **catecholamines** (epinephrine and norepinephrine) by the sympathetic nervous system (SNS). Ultimately, both mediators stimulate the production of reactive oxygen species (**ROS**).

The physiological stress response is one of the mediators of the effects of psychological factors on cancer because of its regulation of the immune system.

Effects on the immune system

Chronic stress reduces lymphocytes and NK cells numbers, and causes shift from Th1 response, the usual one against infected and tumour cells, to Th2.

Sustained activation of negative affective pathways (chronic stress) provide the strongest links to cancer initiation and progression.

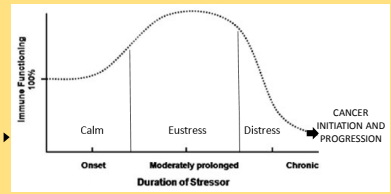


Figure 2. Impairment of immune function under chronic stress [2]

Table 2. Chronic stress mediators signal transduction pathways affecting immune function. TF, Transcription factor; GC, Glucocorticoid; PKA, Protein kinase A; cAMP, Cyclic adenosine monophosphate

Stress mediator	Receptor	Mechanism	Final action
Glucocorticoids	GC receptor (intracellular)	Receptor+GC→ promoters and TF	↑ Anti-inflammatory factors
Catecholamines	β-adrenergic receptor (G-protein)	cAMP→PKA→ TF and protein phosphorylation	↓ Pro-inflammatory factors

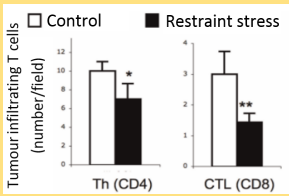


Figure 3. Effects of stress on tumour infiltrating T cells in mice [3]

Impact on cancer initiation and progression

The clinical relevance in human studies of the stress mechanisms remains to be well-characterized

There is growing evidence from *in vitro*, animal and human studies that psychological stress can impact pathways implicated in **solid** cancer onset and progression.

Variables and methodological limitations in human studies

- Risk behaviours
- Immunological assays
- Type and duration of the stressor
- Sex and age
- Small study populations
- Type and stage of cancer

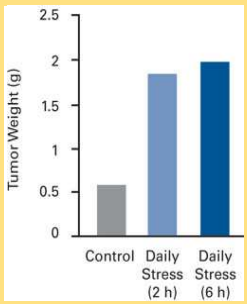
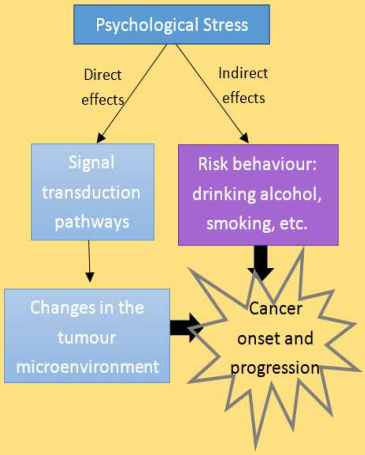


Figure 4. Effects of daily stress on the tumour weight of mice [4]



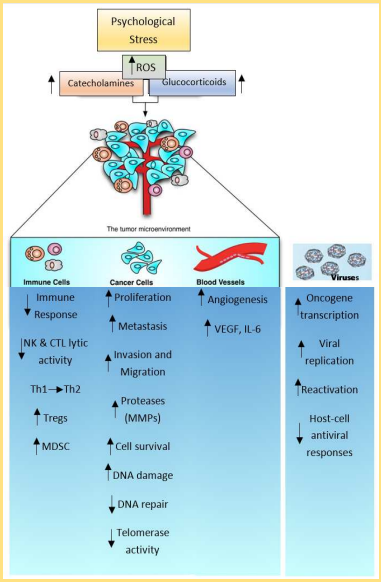
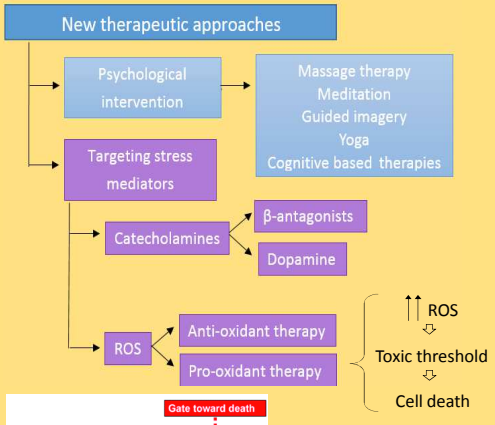
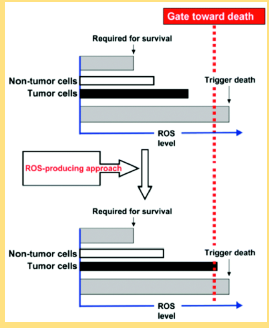


Figure 5. Effects of chronic stress on the tumour microenvironment and on viruses. Adapted from [5]

Clinical implications





Cancer cells have higher ROS content due to accelerated metabolism that renders them more susceptible to oxidative stress-induced cell death than normal cells.

Figure 6. Biological basis for therapeutic selectivity of pro-oxidant therapies [6]

Conclusions

- The pathways involved in the chronic stress impact on cancer are not definitely established in humans due to methodological limitations and several variables.
- Understanding these pathways lead to the development of new therapeutic approaches and the improvement of the ones being currently developed.

Evidence suggests a link between psychological stress and cancer, so further investigation in the field of psychoneuroimmunology would significantly add to the fight against cancer

Future directions

- Future studies will benefit from better articulated hypotheses and prospective design in order to obtain conclusive data.
- Examination of how biobehavioural pathways contribute to effectiveness of chemotherapy and immunomodulatory therapies.
- Personalization: Identification of patients who will benefit most from pharmacologic and psychological interventions.
  - Biological factors
  - Psychological criteria

Main References: 1. Kaminami H *et al.* (2004). Stress, depression, the immune system, and cancer. **2.** McLeod SA. (2010). Stress, Illness and the Immune System. **3.** Dhabhar FS *et al.* (2012). High-Anxious Individuals Show Increased Cancer Progression in a Mouse Model of Squamous Cell Carcinoma. **4.** Thaker PH et al. (2006). Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma. **5.**Sood AK *et al.* (2006). The influence of bio-behavioural factors on tumour biology. **6.** Gérard Audran *et al.* (2014). Alkoxyamines: a new family of pro-drugs against cancer.