Identifying Factors That Cause Cancer to Spread to The Brain and Spinal Cord

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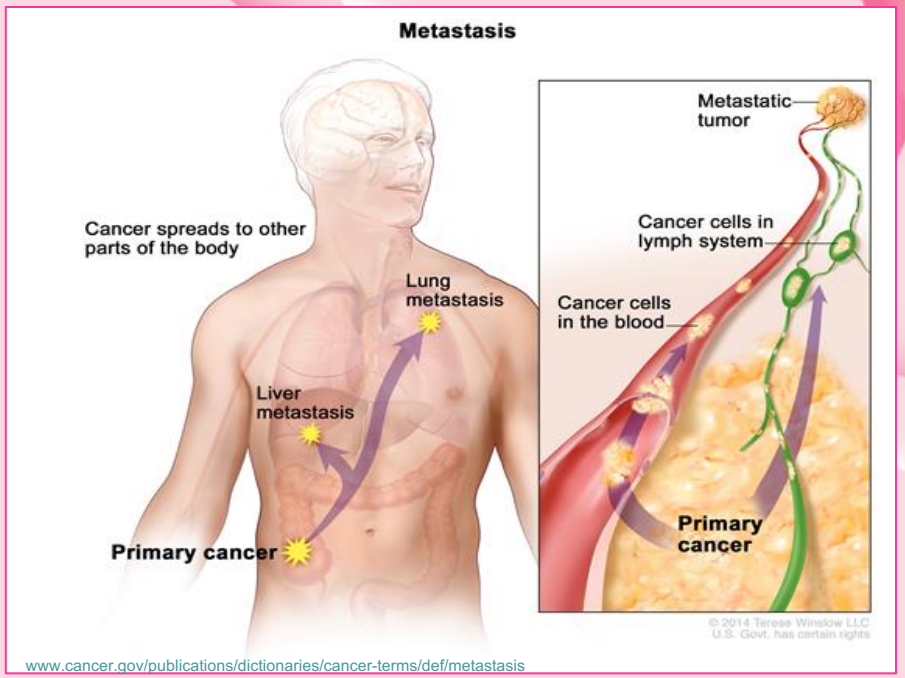
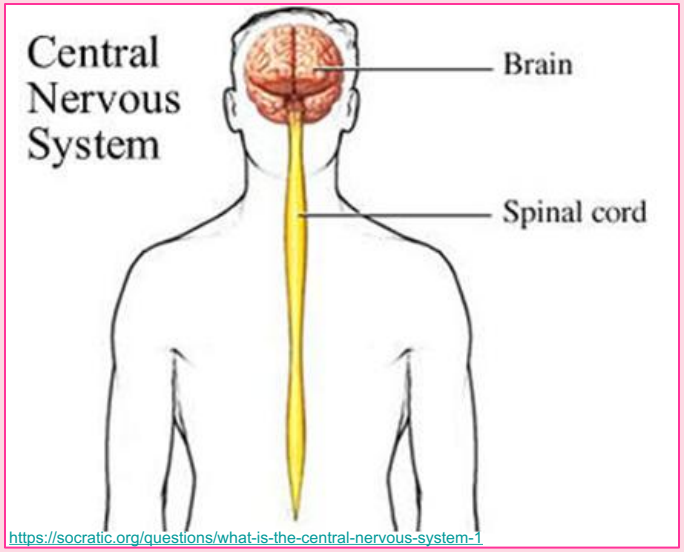
Cancer Metastasis

- Metastasis is the spread of cancer from its primary location to a distant organ
  - It is the cause of 90% of cancer-related deaths



www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis

- Incidence of metastasis to the central nervous system (CNS), i.e. brain & spinal cord has been increasing due to better management of systemic disease
- Most common cancers to metastasize to the CNS are breast, lung & skin



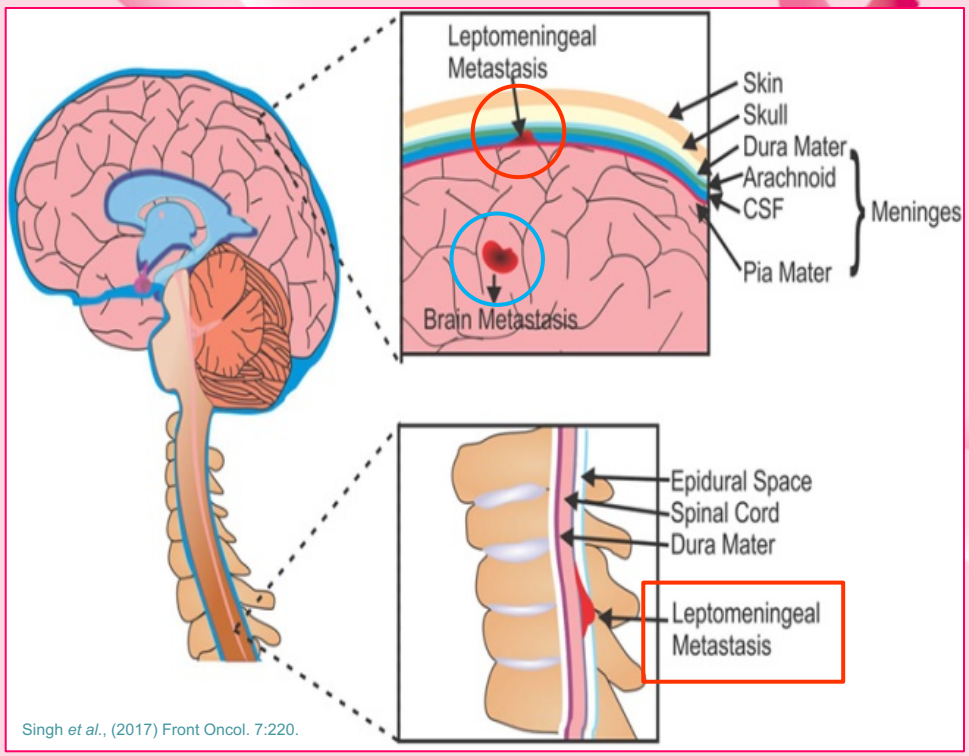
https://socratic.org/questions/what-is-the-central-nervous-system-1

Brain Metastases

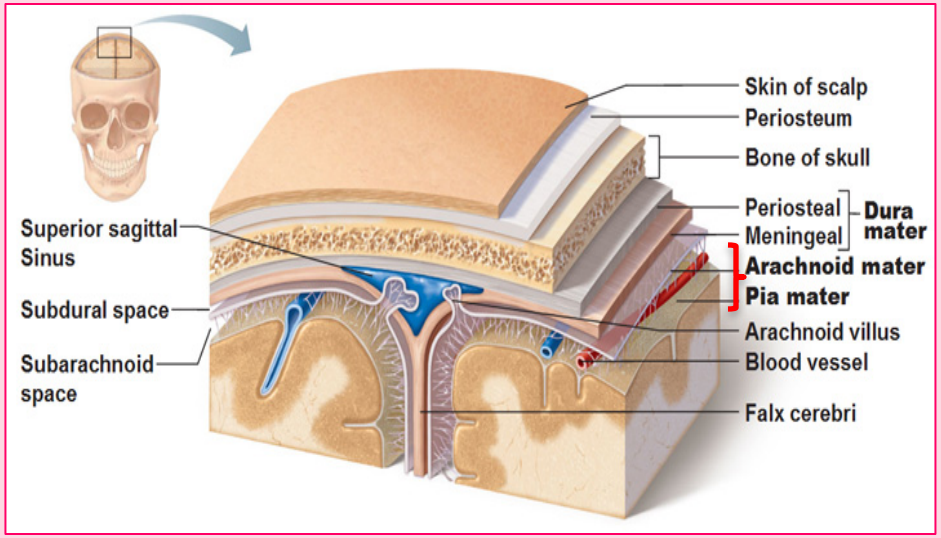
- It is estimated that up to 30% of cancer patients exhibit CNS metastases, which come in 2 types:

1. Parenchymal metastases: form within the brain itself

2. Leptomeningeal metastases: form in the membranes encasing the brain & spinal cord referred to as the leptomeninges



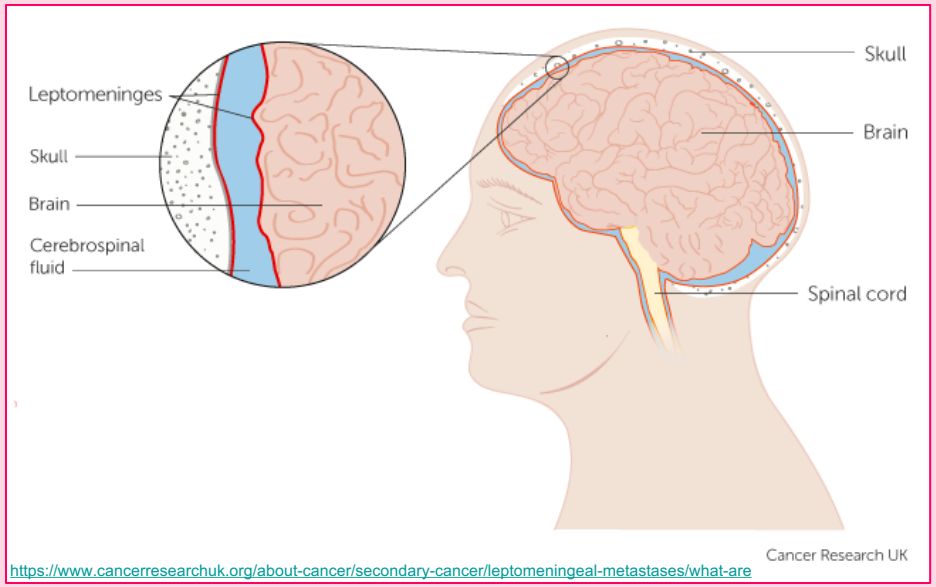
Singh *et al.*, (2017) Front Oncol. 7:220.



Brain Metastases – Patient Prognosis

- **Parenchymal metastases:** are associated with poor prognosis with median survival of treated patients being about 1 year

- **Leptomeningeal metastases:** have a <u>worse outcome</u> → median survival of treated patients is 2 – 4 months
  - **Breast cancer** is among the most common cancers to metastasize to the leptomeninges



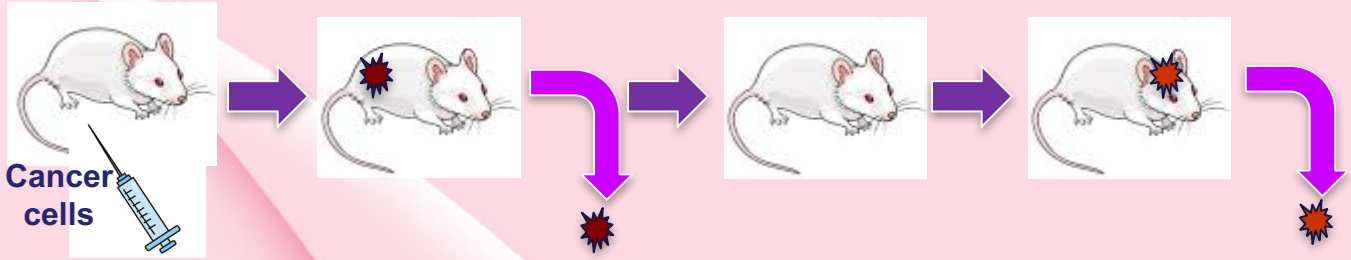
https://www.cancerresearchuk.org/about-cancer/secondary-cancer/leptomeningeal-metastases/what-are

Research on Brain Metastasis

- Parenchymal brain metastases have been extensively investigated by researchers

- Leptomeningeal metastases are greatly understudied by the research community due to lack of animal models that recapitulate the disease experienced by patients

- Fortunately, the Siegel Lab has developed the first 3 animal models that spontaneously form leptomeningeal metastases from tumors grown in the animal breast



Cancer cells are injected in the animal's breast → animal develops breast tumor → breast tumor is resected → animal spontaneously develops leptomeningeal metastases → leptomeningeal tumors are harvested

Preliminary Data From Our Animal Models

- Analysis of one of our animal models (called GCRC1971) revealed the up-regulation of a gene named CIRBP (Cold Inducible RNA Binding Protein)

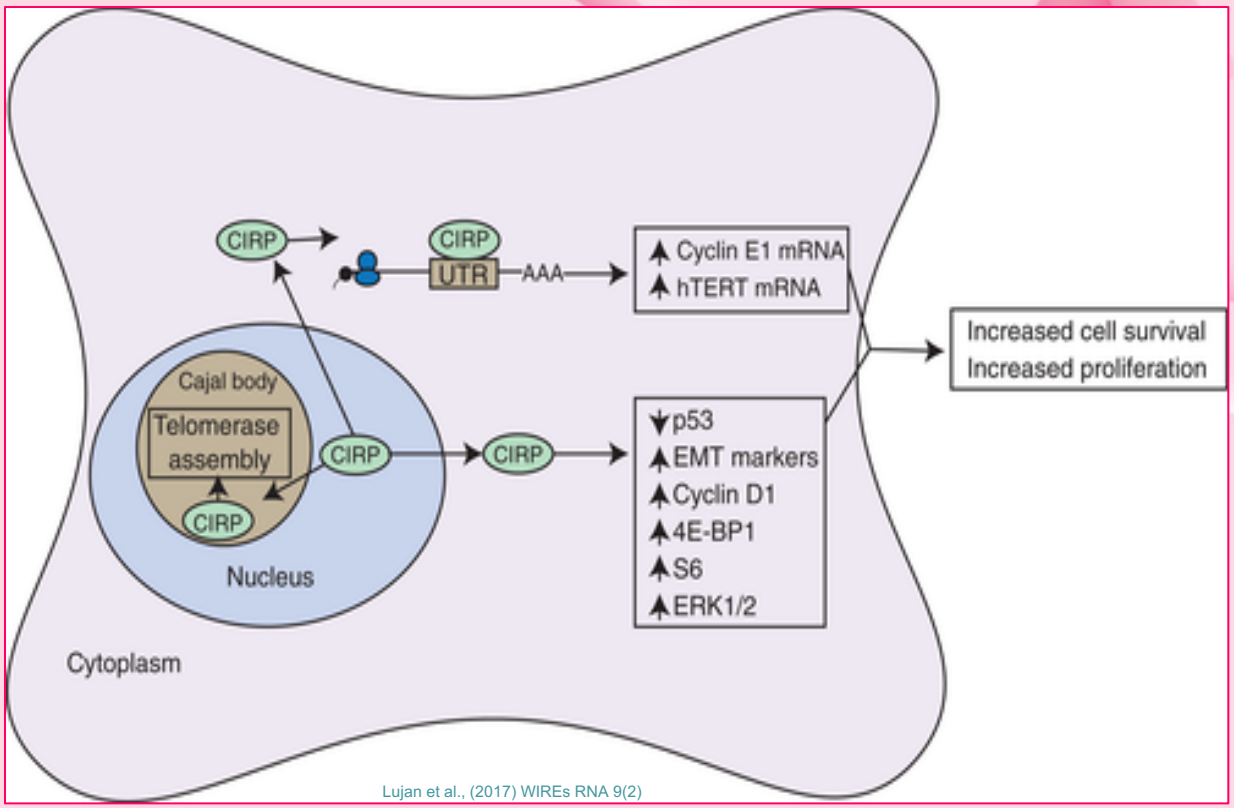
- Our hypothesis: CIRBP is a critical mediator of leptomeningeal metastasis → it allows cancer cells to reach the leptomeninges & survive in their unique environment (the leptomeninges are characterized by low protein & glucose concentrations which constitutes a stressful environment for cells)

Leptomeningeal Metastases vs Primary Mammary Tumor

Upregulated genes	Downregulated genes
RBM3	*FKBP4*
CIRBP	*RP11-1033A18.1*
NGFRAP1	*HSPA8P1*
CTSH	*Hsp110*
S100A4	*Hsc70*
FAM107B	*RP11-144L1.8*
	Hsp70
	NEBL
	FGFR4

How Might CIRBP Promote Leptomeningeal Metastasis?

CIRBP has two structural motifs, called RNP1 & RNP2, that enable it to bind its targets which in turn allow cancer cells to survive in the stressful environment of the leptomeninges



Lujan et al., (2017) WIREs RNA 9(2)

RNP2 RNP1

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1   – MASDEGKLFVGGLSFDTNEQALEQVSFSKYGQISEVVVVKDRETQRSRGFGFVTFENIDDA –60
61  – KDAMMAMNGKSVDGRQIRVDQAGKSSDNRSRGYRGGSAGGRGFFRGGRSRGRGFSRGGGDR –120
121 – GYGGGRFESRSGGYGGSRDYYASRSQGGSYGYRSSGGSYRDSYDSYATHNE          –172
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Research Project Aims & Impact

- **AIM1:** Elucidate the mechanism of action of CIRBP
  → Will be achieved by modulating the level of expression of CIRBP in the animal models & in cell lines and the consequent impact on the formation of leptomeningeal metastases will be investigated

- **AIM2:** Identify the targets that CIRBP binds to in the process
  → Identify molecular targets that CIRBP binds in breast tumors & in leptomeningeal metastases

- **Impact:** Resulting knowledge can be ultimately employed to establish therapeutic strategies in order to treat or prevent leptomeningeal metastasis which is associated with extremely poor prognosis for thousands of Canadians & worldwide patients annually

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