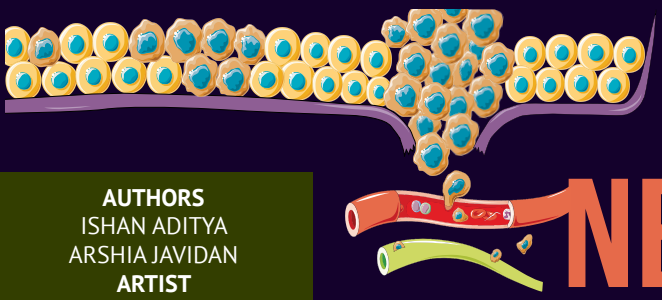
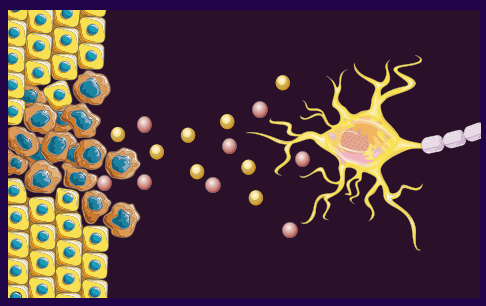


PATHOPROFILE
NEO-NEUROGENESIS

AUTHORS
ISHAN ADITYA
ARSHIA JAVIDAN
ARTIST
CABERRY WEIYANG YU

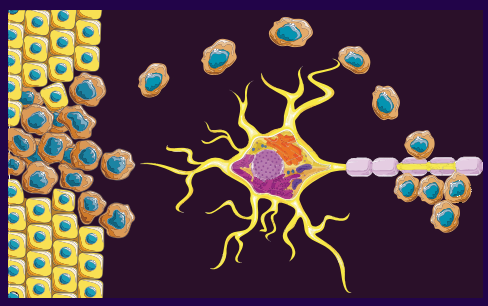
INTRODUCTION

Cancer is a disease characterized by the abnormal proliferation of cells in different parts of the body.[1] Cells grow uncontrollably and form malignant masses of tissues known as tumours. Cancerous tumours are malignant, meaning that they can spread into nearby tissues. In the process of metastasis, some cancer cells may break off from the original tumour and travel through the bloodstream or the lymphatic system to form new tumours.[1] These metastatic tumours develop their own vasculature via neo-angiogenesis and tumour innervation leads to heightened sensitivity and pain.



NEO-NEUROGENESIS

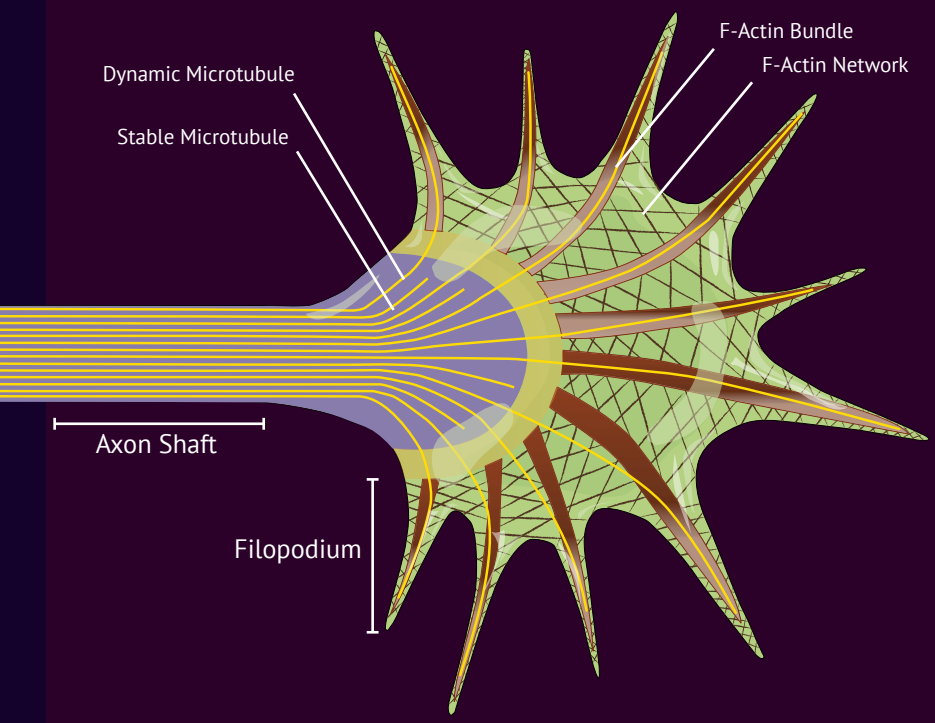
Neo-neurogenesis is a process resulting in tumour innervation due to factors sectreted by tumour cells that initiate stem cell differentiation into neurons.[1] During neo-neurogenesis, cancer cells release signaling molecules known as chemotropic cues that act on nearby neurons to direct their growth towards the tumour.



PERINEURAL INVASION

Through a process known as perineural invasion, cancer cells infiltrate neurons and migrate to distant sites.[1] There is a reciprocal interaction between cancer cells and neurons, wherein cancer cells secrete signals that cause neuronal growth and neurons secrete signals that can enhance cancer cell proliferation.

GENERAL ANATOMY & PHYSIOLOGY OF THE AXON



Axonal growth is necessary to form neuronal connections in order to facilitate communication in the human body.[2] During axonal growth, the neuron extends its axon to reach a specific destination. Axon growth occurs through the growth cone, located at the tip of the axon, via growth cone advancement.[3] Formed from actin bundles, filopodia are located at the axon terminus and are finger-like projections that detect the surrounding environment.

Microtubules comprise the main part of the axon and are mostly found as stable bundles at the core.[3] Dynamic microtubules project into peripheries and their function is to detect the surrounding environment via the filopodia.

Growth cone advancement involves a balance between actin polymerization for protrusion and retrograde flow for retraction. Polymerization involves linking actin monomers to form actin polymers. [4] Actin Retrograde flow is the movement of actin back to the core of the growth cone, mediated by actin-myosin contractions.[5] Both protrusion and retraction are important for growth cone movement.

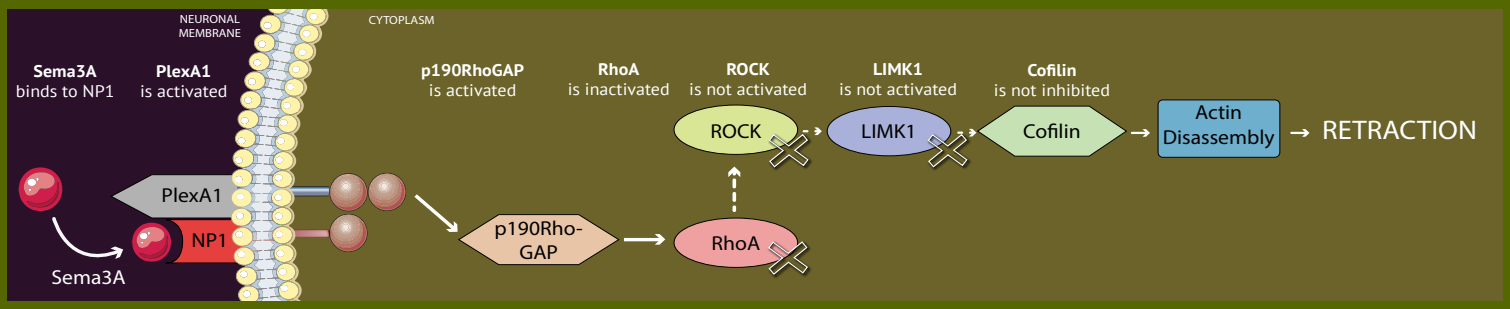
1. Mancino M, Ametller E, Gascón P, Almendro V. The neuronal influence on tumor progression. Biochimica et Biophysica Acta (BBA) - Reviews on Cancer. 2011;1816(2):105-118
2. Lowery LA, Van Vactor D. The trip of the tip: understanding the growth cone machinery. Nat Rev Mol Cell Biol. 2009 May;10(5):332–43.
3. Medeiros NA, Burnette DT, Forscher P. Myosin II functions in actin-bundle turnover in neuronal growth cones. Nat Cell Biol. 2006 Mar;8(3):215–26.
4. Schaefer AW, Kabir N, Forscher P. Filopodia and actin arcs guide the assembly and transport of two populations of microtubules with unique dynamic parameters in neuronal growth cones. J Cell Biol. 2002 Jul 8;158(1):139–52.
5. Kalil K, Li L, Hutchins BI. Signaling mechanisms in cortical axon growth, guidance, and branching. Front Neuroanat. 2011;5:62.
6. Barberis D, Casazza A, Sordella R, Corso S, Artigiani S, Settleman J, et al. p190 Rho-GTPase activating protein associates with plexins and it is required for semaphorin signalling. J Cell Sci. 2005 Oct 15;118(Pt 20):4689–700.
7. Gallo G. RhoA-kinase coordinates F-actin organization and myosin II activity during semaphorin-3A-induced axon retraction. J Cell Sci. 2006 Aug 15;119(Pt 16):3413–23.
8. Neufeld G, Kessler O. The semaphorins: versatile regulators of tumour progression and tumour angiogenesis. Nat Rev Cancer. 2008 Aug;8(8):632–45.
9. McGough A. Cofilin Changes the Twist of F-Actin: Implications for Actin Filament Dynamics and Cellular Function. The Journal of Cell Biology. 1997;138(4):771-781.
10. Lebrand C, Dent EW, Strasser GA, Lanier LM, Krause M, Svitkina TM, et al. Critical role of Ena/VASP proteins for filopodia formation in neurons and in function downstream of netrin-1. Neuron. 2004 Apr 8;42(1):37–49.
11. Gomez T, Robles E. The Great Escape. Neuron. 2004;42(1):1-3.

CANCER-MEDIATED AXONAL GROWTH: OVERVIEW

Tumours direct growth cone navigation by secreting chemotropic cues, which may act as attractive or repulsive signals.[4] These molecules, including semaphorins and netrins, play a role in axon guidance by regulating actin dynamics. This occurs through signaling involving the Rho family of GT-Pases. The Rho GTPases are G-proteins that control cytoskeletal rearrangements to promote either protrusion or retraction.

ALTERNATE PATHWAY OF AXON GROWTH: RETRACTION VIA SEMAPHORINS

1. There are a variety of semaphorins. Class 3 semaphorins (Sema3A) are found in vertebrates and bind to neuropilin 1 (NP1), activating a receptor called plexA1. NP1 is part of a preformed complex with PlexA1.[6]
2. In absence of semaphorin, the sema domain of plexA1, which is semaphorin-specific, auto-inhibits activation of the plexA1 receptor via phosphorylation.
3. Binding of semaphorin to NP1 induces a conformational change in the plexin that removes this auto-inhibition, resulting in the activation of plexA1.[7]
4. This binding activates p190 Rho-GTPase activating protein (p190RhoGAP), which then inactivates Ras homolog gene family member A (RhoA), a Rho GTPase, via hydrolysis of GTP to GDP.
5. Normally, RhoA activates Rho-associated protein kinase (ROCK) via phosphorylation, which in turn activates LIM domain kinase 1 (LIMK1).[8] However, since RhoA has been inactivated by p190RhoGAP, ROCK and LIMK1 are also left inactivated.
6. LIMK1 is responsible for inhibiting the actin-degrading enzyme cofilin via phosphorylation.[9] In the absence of active LIMK1, cofilin is activated.



PATHWAY OF AXON GROWTH: NETRINS

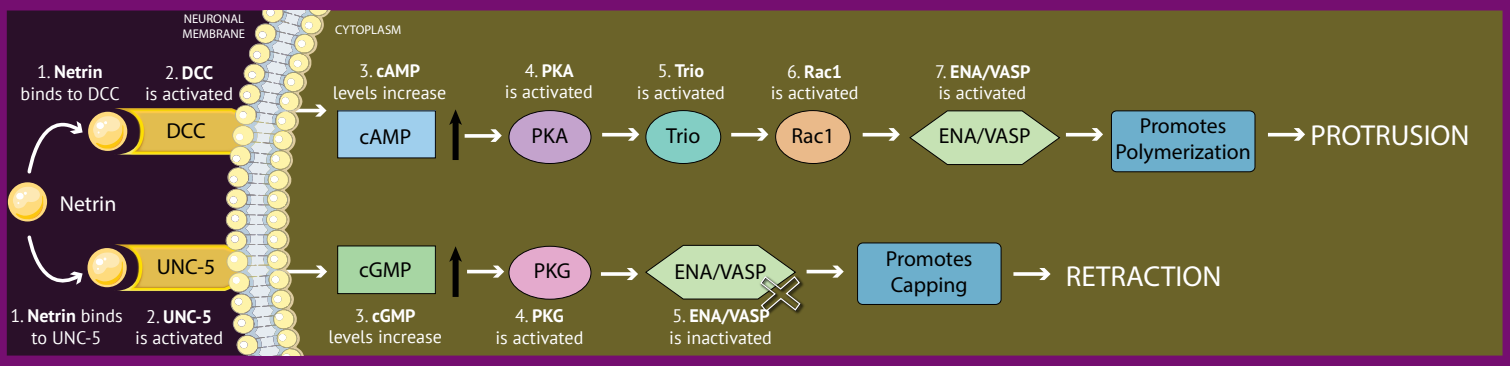
Depending on which receptors they activate, netrins promote either protrusion or retraction. Netrins interact with the deleted in colorectal cancer (DCC) receptor to cause chemoattraction, and they interact with UNC-5 receptors to cause chemorepulsion.[10]

Protrusion: Activation of DCC Receptor

1. Binding of netrins to the DCC receptor elevates cAMP levels, thus activating **protein kinase A (PKA)** via phosphorylation. In turn, PKA activates triple domain binding protein (Trio).[11]
2. Trio then activates the Rho GTPase Rac1.
3. Rac1 targets downstream effectors involved in cytoskeletal remodeling, which include ENA/VASP proteins, which promote protrusion.[12]
4. However, PKA itself can also activate ENA/VASP without going through the Rho GTPase pathway.

Retraction: Activation of UNC-5 Receptor

1. Binding of netrins to the UNC receptor **elevates cGMP** levels.[13]
2. This activates **protein kinase G (PKA),** which inactivates ENA/VASP proteins via phosphorylation.
3. This promotes capping which involves the cessation of actin polymerization, resulting in retraction.[14]



How Does Cancer Promote Synaptogenesis and Neurotransmission?

Netrins increase the probability of axon and dendrite contact by increasing filopodia and promoting filopodial elongation.[15] They cause recruitment of synaptic proteins synapsin and synaptophysin.[16] Synapsin allows synaptic vesicles to be released from nerve terminal during action potentials while synaptophysin recruits and interacts with synaptobrevin, a SNARE protein involved in exocytosis.[17] These two proteins ultimately result in increased neurotransmission via the formation of synapses.

CONCLUSION

Understanding the dynamics of neo-neurogenesis brings us one step closer to gaining a holistic understanding of cancer physiology,. This enables us to develop treatments to mitigate the devastating effects of this condition.

12. O'Connor K, Mercurio A. Protein Kinase A Regulates Rac and Is Required for the Growth Factor-stimulated Migration of Carcinoma Cells. The Journal of Biological Chemistry. 2001;276(51):47895–47900.
13. Barzik M, Kotova T, Higgs H, Hazelwood L, Hanein D, Gertler F et al. Ena/VASP Proteins Enhance Actin Polymerization in the Presence of Barbed End Capping Proteins. Journal of Biological Chemistry. 2005;280(31):28653-28662.
14. Chereau D, Dominguez R. Understanding the role of the G-actin-binding domain of Ena/VASP in actin assembly. Journal of Structural Biology. 2006;155(2):195-201.
15. Goldman J, Ashour M, Magdesian M, Tritsch N, Harris S, Christofi N. Netrin-1 Promotes Excitatory Synaptogenesis between Cortical Neurons by Initiating Synapse Assembly. Journal of Neuroscience. 2013;33(44):17278-17289.
16. Stavoe A, Colon-Ramos D. Netrin instructs synaptic vesicle clustering through Rac GTPase, MIG-10, and the actin cytoskeleton. The Journal of Cell Biology. 2012;197(1):75-88.
17. Kwon S, Chapman E. Synaptophysin Regulates the Kinetics of Synaptic Vesicle Endocytosis in Central Neurons. Neuron. 2011;70(5):847-854.
18. Luk T. An Investigation of the Role for Netrin-1 and the Netrin Receptor Deleted in Colorectal Cancer in Regulating Dendritic Spine Morphology. M.Sc. Neuroscience. Department of Neurology and Neurosurgery: McGill University; 2007.