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in support of WORLD CANCER RESEARCH DAY

September 24th

2024 Campaign

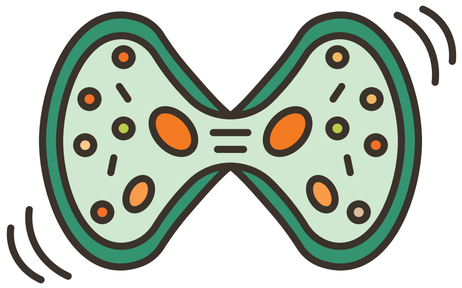
INNOVATION IN CANCER RESEARCH DRIVES PROGRESS TOWARDS HEALTH EQUITY

HedgeHog signalling pathway and cancer

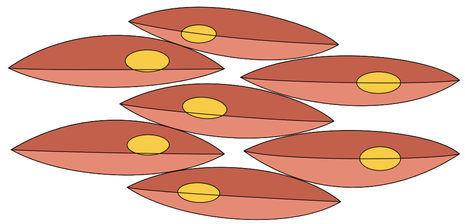
By Dr Hafsa Waseela Abbas

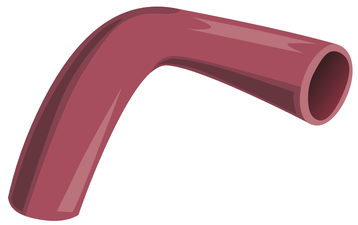
FUNCTIONS OF THE HEDGEHOG SIGNALLING PATHWAY

- Cell proliferation
- Cell cycle regulation
- Cell division
- Mitogenesis
- angiogenesis
- Differentiation of cells and tissues into the brain, heart, muscles, and other systems.
- Tissue polarity of the embryo



(Macarulla Mercade *et al*., 2024)





GLOSSARY

- **Angiogenesis** - The production of new blood vessels for cells to receive the nutrients to function.
- **Cell division** - The process in which the parental cell divides into two daughter cells where the nucleus and contents in the cytoplasm are equally divided (Ong and Torres, 2019).
- **Cell proliferation** – The increased growth/number of cells
- **Differentiation** – Changes to cell shape and function when unspecialized cells become specialized for specific functions.
- **Embryo** - The early phase of growth and development in mammals.
- **Tissue polarity** - The uneven distribution of proteins, and organelles (parts of a cell) in different forms. It is important in how cells divide, develop, and differentiate to form tissues. (Nelson, 2003).

Farah With Me Cancer Project is part of Farah Saeed Trust, a voluntary organisation that aims to inspire, educate and help others. Farah With Me aims to raise public awareness on cancer through virtual and in-person event. World Cancer Research Day is not affliiated with FST, however, FST enjoys partaking in its annual research initiatives.

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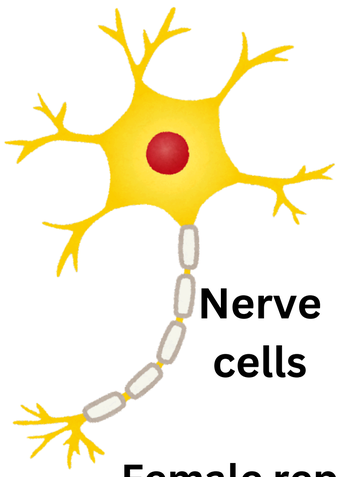
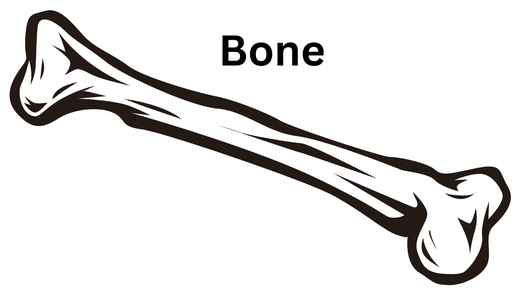
WHAT IS A HEDGEHOG?

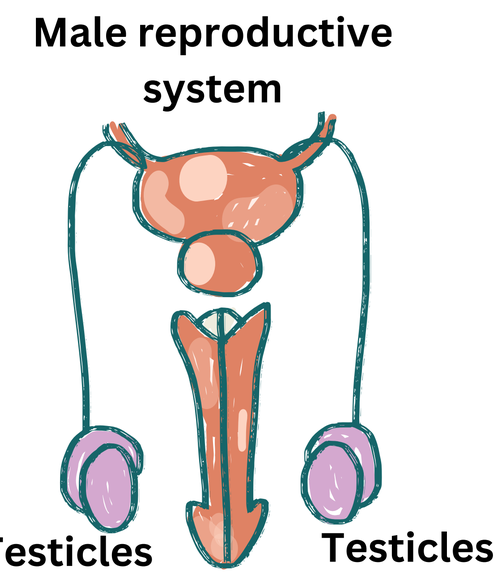
Hedgehog is a ligand and there are three main types of Hedgehog ligands that activate Hedgehog signalling but vary in the transcription of the target genes:

1. **Sonic Hh [SHh]: nerve cells and limbs where they are commonly found.**
2. **Indian Hh [IHh]: skeletal development especially ossification of echondrocytes.**
3. **Desert Hh [DHh]): gonads, granulosa cells of ovaries, Sertoli cells of testis.**

(Davis, 2024; Shen *et al.*, 2024; Carballo *et al.*, 2018; Akyala and Peppelenbosch, 2018)







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GLOSSARY FOR PAGE 2

- **Echondrocytes** - It is found in connective tissue such as the cartilage tissue and it produces growth factors and enzymes that regulate the production of the extracellular matrix. They are originally found inside the bone (bone marrow). Cartilage is needed to protect movements in the joint. There is limited to do if the liver is damaged. (Chen et al. 2021)
- **Gonads** – Male and female reproductive systems that produce the sex cells.
- **Granulosa cells of ovaries** - It is found in the female reproductive system where it functions in producing the hormones, follicular development (maturation of the egg cell), and in the release of the egg(ovulation) to fertilize with the male sex cell (Cleveland Clinic, 2022).
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Sertoli cells of testis** – Cells found in the walls of the testis, particularly in loop-shaped structures called seminiferous tubules.
- **Transcription** - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA)..

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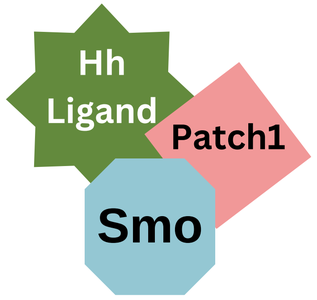
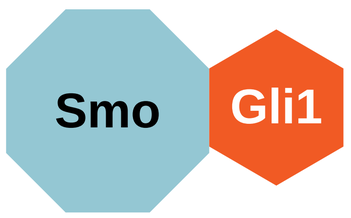
AN OVERVIEW OF THE HEDGEHOG SIGNALLING PATHWAY

1 The Hedgehog Ligand (Sonic, Indian, or Desert Hedgehog) joins with its specific receptor; Patched-1 receptor.

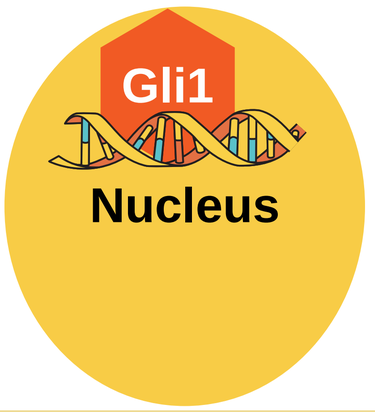
2 Another receptor called Smoothened receptor (Smo) is activated in response to the Hedgehog-Patched1 binding.



3 Smoothened receptor activates the Glioma-associated oncogene homolog 1 (Gli1) transcription factor.



4 The activation of Gli1 leads to the transcription of Hedgehog target genes e.g. GLI1 and Patched-1, and other genes that regulate the cell cycle.



(Van Hoff *et al*., 2009; Farberg *et al*., 2024)

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GLOSSARY FOR PAGE 4

- **Cell cycle** - The process in which cells (plants and animals and other eukaryotic cells) grow and divide.
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Nucleus** - It is a structure found within the cell where it contains genetic material to control the cell.
- **Oncogene** - A gene that has been mutated and when overexpressed, it promotes cancer growth and progression.
- **Receptor** - A type of protein that can recognize its signaling molecule e.g. A ligand.
- **Transcription** - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).
- **Transcription factor** - A protein that helps transcribe genes by affecting the enzyme RNA polymerase.

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A FURTHER INSIGHT INTO THE HEDGEHOG SIGNALLING PATHWAY

There are two pathways: canonical and non-canonical.

Canonical pathway – HEDGEHOG ON

The Sonic Hedgehog (SHh) ligand is a glycoprotein. It binds to the protein receptor (Patch) and inactivates it. There are two types of Patch receptors: Patch 1 (Ptch1) and Patch 2 (Ptch2). The structure of Ptch2 shares 54% similarity with the structure of Ptch1 but vary in where in its expression and how it communicates (signalling).

→

The binding of the SHh ligand with Ptch1 receptor regulates the (Smoothened) Smo protein.

The Smo is a seven-transmembrane GPCR-like protein found in the vesicle.

→

The Smo is not inhibited by Ptch1.

→

Ptch1 is targeted for degradation by the proteosome.

↓

The levels of Smo increases and accumulates at the plasma membrane which starts further signalling and transcription of target genes.

←

Smo also activates Glioma-associated oncogene homolog 1 (Gli1).

Gli are zinc-finger transcription factors found in vertebrates and depend on the Hedgehog ligand

There are three subtypes:

Gli1 – transcriptional activator

Gli2 – act either negative or positive regulators.

Gli3 – act either negative or positive regulators.

←

Gli1 translocates into the nucleus where it activates target genes: PTCH1, PTCH2 and Gli1 genes.

←

Smo also activates Glioma-associated oncogene homolog 1 (Gli1).

↓

Gli protein also modulates Wnt and Noggin proteins in head and limb development (Karunaraj *et al.* 2022)

(Davis, 2024; Shen *et al.*, 2024; Carballo *et al.*, 2018; Akyala and Peppelenbosch, 2018)

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GLOSSARY FOR PAGE 6

- **Canonical pathway** – It is a process that has common features in an established or specific manner. However, when a new feature does not fit or partially fit in the established way is considered as non-canonical pathway (Biosynthesis, 2021)
- **Cell** – The simplest unit of a living organism.
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Glioma** - cancer of the glial cells that surround the nerve cells in the brain and spinal cord.
- **G protein-coupled receptors (GPCRS)** - They are receptor proteins found on the cell surface. They mediate lots of roles that are triggered by signals outside the cell, for instance, fat molecules, hormones, small proteins, and neurotransmitters (chemicals) (Zhang *et al*. 2023)
- **Glycoprotein** – A protein that is attached to a carbohydrate group.
- **Homolog** – A similar structured protein and its genetic sequence encoding it. It also refers to homology applied between DIC and vice (Boundless. 2024)
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Nucleus** - It is a structure found within the cell where it contains genetic material to control the cell.
- **Oncogene** - A gene that has been mutated and when overexpressed, it promotes cancer growth and progression.Protein - A large molecule that is made of amino acids joined together
- **Proteosome** - A structure found in the cell that degrades proteins.
- **Receptor** - A type of A type of protein that can recognize its signaling molecule e.g. A ligand.
- **Transcription** - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).
- **Transcription factor** - A protein that helps transcribe genes by affecting the enzyme RNA polymerase.
- **Transmembrane protein** - It is a protein found integral in the membrane where it functions as a receptor, transporter, and ion channel through the double layer of fat in the membrane to transport molecules and ions across the membrane (Senju and Suetsugu, 2023).
- **Vesicles** - A small structure or sac filled with fluid or gas and is surrounded with a membrane. Its role is to store and transport products found in the cells, digest wastes from metabolic reactions (BiologyOnline, 2024)

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A FURTHER INSIGHT INTO THE HEDGEHOG SIGNALLING PATHWAY

Canonical pathway – HEDGEHOG OFF

1. In the absence of Shh ligand, Ptch1 inhibits Smo protein.
2. Gli protein is phosphorylated and become Gli repressor (Gli-R) proteins.
3. The Gli-R proteins translocate into the nucleus where it represses all the Hedgehog target genes (stop transcription. This is known as graded signalling where the number of GLli-R and Gli proteins within a cell is important and depends on how much Hh protein is produced and genes expressed.

GLOSSARY

- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Nucleus** - It is a structure found within the cell where it contains genetic material to control the cell.
- **Phosphorylation** - The process where a phosphate group is added to a molecule.
- **Protein** - A large molecule that is made of amino acids joined together.

(Davis, 2024; Shen *et al.*, 2024; Carballo *et al.*, 2018; Akyala and Peppelenbosch, 2018)

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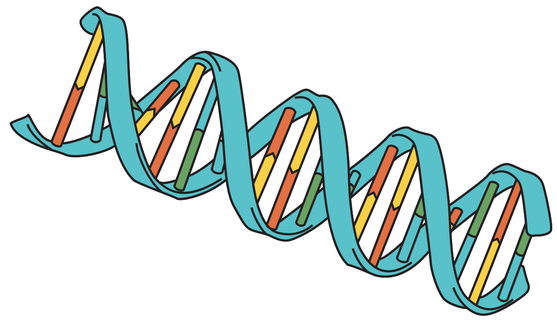
HOW DOES GLI PROTEINS REGULATE THE CANONICAL HEDGEHOG PATHWAY?

1. Gli2 activated (Gli2A) or Gli2 repressor (Gli2R).
2. Gli2A can accumulate to control transcriptional activation in response to Hedgehog-Ptch1 binding – This helps overcome negative regulation of Gli3.
3. Gli2 activated (Gli3A) or Gli3 repressor (Gli3R). The transformation from GLI3A to Gli3R helps Gli2 to function.
4. However, when Shh binds to Ptch and activates Smo – Smo converts Gli3R into an activated form (Gli3A).



5. Gli1 and Gli2 can be acetylated at the amino acid residues: lysine 518 and 757, respectively.
6. The enzyme histone deacetylase 1 (HDAC1) deacetylates Gli proteins to help increase transcriptional activation.
7. This activation is turned off by the degradation of HDAC1, which sustains a positive autoregulatory loop, when Shh is present.
8. The degradation is mediated through an E3 ubiquitin ligase complex.

(Davis, 2024; Shen *et al.*, 2024; Carballo *et al.*, 2018; Akyala and Peppelenbosch, 2018)

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GLOSSARY FOR PAGE 9

- **Acetylation – the addition of the acetyl group C_2H_3O and this occurs to stabilize proteins, activity of enzymes, protein-protein interaction, protein-DNA interactions, transcription, and regulate kinase enzyme activity (Shang, Liu, and Hua, 2022)**
- **Amino acid - The building blocks of proteins. It has a carboxyl group (COOH), and an amine group (NH2), Between them is a hydrogen atom and an R group (specific side chain).**
- **Protein - A large molecule that is made of amino acids joined together.**
- **Repressor – Negative regulation that occurs in target genes where a transcription factor prevents transcription by connecting with the DNA.**
- **Transcription - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).**
- **Transcription factor - A protein that helps transcribe genes by affecting the enzyme RNA polymerase.**
- **Ubiquitin – a small peptide (short chain of amino acids) binds to proteins that are scheduled to under proteolysis.**
- **Ubiquitin E3 ligase - It is an enzyme that increases ubiquitination and degradation (Zheng and Shabek, 2017).**

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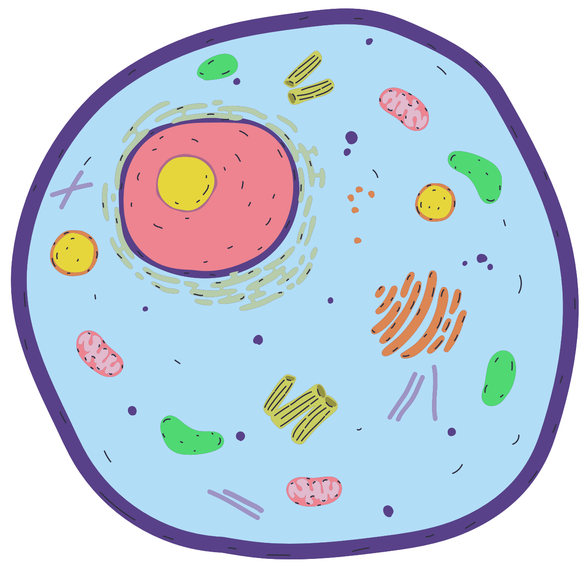
NEGATIVE REGULATION OF THE HEDGEHOG CANONICAL PATHWAY

Supressor of Fused (SUFU) regulation is a negative regulator of the Shh signalling pathway.

It binds directly to the Gli proteins where SUFU undergoes hyper phosphorylation for Gli-R proteins to be formed.

This halts their translocation to the nucleus to induce transcription of Hedgehog target genes e.g Ptch1 and Gli1

Gli-R forms remain in the cytoplasm by SUFU where it is then degraded which prevents Hedgehog signalling.



Gli-R proteins are phosphorylated by the following enzymes:

- glycogen synthase kinase 3 beta (GSK3β)
- casein kinase I (CK1)
- protein kinase A (PKA)

Gli-R forms as a result of these phosphorylation remain in the cytoplasm by SUFU where it is then degraded which prevents Hedgehog signalling.

(Teglund and Toftgard, 2010; Carballo *et al.*, 2018)

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GLOSSARY FOR PAGE 11

- **Enzyme** - A type of protein that speeds up a chemical reaction.
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Nucleus** - It is a structure found within the cell where it contains genetic material to control the cell.
- **Phosphorylation** - The process where a phosphate group is added to a molecule.
- **Protein** - A large molecule that is made of amino acids joined together.
- **Repressor** – Negative regulation that occurs in target genes where a transcription factor prevents transcription by connecting with the DNA.
- **Transcription** - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).

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OTHER KEY REGULATORS THAT MODULATE THE CANONICAL HEDGEHOG PATHWAY AT DIFFERENT LEVELS

Kif7 is an kinesin-4 family protein in vertebrates is a regulator of the Hedgehog signalling pathway and a ciliopathy protein localise in the cilium. It limits the length anf controls the structure of the cilium. The Gli-SUFU activity to be regulated (He *et al*., 2014)

Fused (Fu) protein is a regulator of the Hedgehog signalling. It is a protein kinase that binds to the kinesin protein Costal-2 (Cos2). It is not found in mammalian cells but with Drosophila in the species D. melanogaster and also in mice but in the latter known as Stk36 (Wilson *et al*. 2009; Briscoe and Thérond, 2013)

- Protein kinase C enzyme
- · Mitogen activated protein kinase kinase (Mek1), enzyme.
- · Phosphoinositide-3 kinase (PI3K) enzyme
- · Yak1-related kinase (DYRK1) enzyme

(Carballo *et al*., 2018)

GLOSSARY

- Cell – The simplest unit of a living organism.
- Cilium – They are small hair-like structure found outside the cell whose role involves movement of the cell..
- Drosophilia – Type of fruit fly
- Enzyme - A type of protein that speeds up a chemical reaction.
- Kinesin - A motor protein found in proteins in the cytoskeleton where it functions in movement, transport, shape, and cell division (Ali and Zhang, 2020).
- Protein - A large molecule that is made of amino acids joined together.
- Vertebrates – Animals with a backbone.

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A FURTHER INSIGHT INTO THE HEDGEHOG SIGNALLING PATHWAY

There are two pathways: canonical and non-canonical.

Non-Canonical pathway - They do not depend on Gli proteins and have two types of pathways

(Davis, 2024; Shen *et al.*, 2024; Carballo *et al.*, 2018; Akyala and Peppelenbosch, 2018)

TYPE 1

Aim: It modulates calcium ions (Ca2+ and the actin cytoskeleton via Smo protein

1. The Hedgehog ligand binds to the Patch receptor.
2. Smo protein is not inhibited.
3. Smo protein connected with G-proteins (Gi)
4. Small GTPase enzymes, RhoA and Rac1 are activated causing a Warburg effect.
5. Smo protein stimulates calcium ions from a structure called endoplasmic reticulum.
6. The enzyme Phospholipase C (PLC-γ) catalyses the opening of channels by forming the chemical inositol triphosphate (IP3).
7. The α-tubulin undergoes acetylation by the calcium ions. This functions in chemotaxis and cell migration

TYPE 2

1. It does not rely on Smo protein.
2. Cyclin B1 interaction with Ptch is stopped when the Hedgehog ligand binds with Ptch instead.
3. This causes an increase in cell proliferation and survival.

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GLOSSARY FOR PAGE 14

- **Alpha (α) tubulin** – One of the subtypes of the protein tubulin that forms the hollow-shaped protein structures in the cytoskeleton. It provides support, and transport and helps in how cells grow and divide. It is commonly overexpressed in the nucleus of cancer cells and resistant to undergo apoptosis (Binarova and Tuszynski).
- **Cell proliferation** – The increased growth/number of cells
- **Chemotaxis** - The movement of different types of cells by chemical gradients outside the cell. Chemotaxis is needed to recruit white blood cells to the injury site, and development of the nervous system. Improper cell movement can cause tumor growth, metastasis, and inflammation (Jin, Xu, and Hereld, 2008)
- **Enzyme** - A type of protein that speeds up a chemical reaction.
- **Cyclin** – A protein that facilitates the cell to go through the cell cycle by binding to a cyclin-dependent kinase.
- **Cytoskeleton** - a structure consisting of three proteins – microtubules, actin of intermediate filaments.
- **Endoplasmic reticulum** - A network of membranes in the cell's cytoplasm that create fluid-filled tubules. It is where proteins are made, transported, and folded. It is also involved in producing fat and carbohydrate metabolism. (Schwarz and Blower, 2016)
- **G proteins** – a protein found inside the cell where it can bind to two molecules guanosine triphosphate (GTP) and guanosine diphosphate (GDP) that participate in cell signaling
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Protein** - A large molecule that is made of amino acids joined together.
- **Receptor** - A type of protein that can recognize its signaling molecule e.g. A ligand.

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CROSS TALK BETWEEN CANONICAL AND NON-CANONICAL PATHWAYS

A protein called Intraflagellar transport protein 80 (IFT80) promotes Hh canonical signaling.

How?

It activates Hedgehog-Smoothened-Patch1-Glioma-associated oncogene homolog 1 (Hh-Smo-Ptch1-Gli) signaling pathway during osteoblasts (OBs) differentiation.

Non-canonical Hedgehog (Hh) negatively regulates OB differentiation.

How?

It is inhibited via the Hedgehog-Smoothened-Gprotein-Ras homolog family member A (Hh-Smo-Gαi-RhoA) signalling pathway.

There is also evidence of Cross-talk with other pathways like transforming growth factor beta (TGFßs), Wnt, Notch and Shh.

(Davis, 2024; Shen *et al*., 2024; Carballo *et al*., 2018; Akyala and Peppelenbosch, 2018)

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GLOSSARY FOR PAGE 16

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- **Differentiation** – Changes to cell shape and function when unspecialized cells become specialized for specific functions.
- **Homolog** – A similar structured protein and its genetic sequence encoding it. It also refers to homology applied between DIC and vice (Boundless. 2024)
- **Oncogene** - A gene that has been mutated and when overexpressed, it promotes cancer growth and progression.
- **Osteoblasts** – The type of cells that produce bone and is found in the early phases of the baby (embryo)
- **Protein** - A large molecule that is made of amino acids joined together.
- **Receptor** - A type of protein that can recognize its signaling molecule e.g. A ligand.

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MUTATIONS IN THE GENES INVOLVED IN THE HEDGEHOG SIGNALLING PATHWAY

Overexpression of the Hedgehog ligand through autocrine or paracrine signalling can cause cancer

Mutati.ons can inhibit tumour suppressor genes or increase transcription of genes can cause cancer

Example 1

Downregulation of Patched protein suppresses the transcription of genes in cell growth and development. This keeps the Hedgehog signalling pathway to continuously function causing cancer cell growth and progression.

Example 2

Gain of function mutations e.g. Smoothened protein. This lead to dysregulation of canonical pathway and continuous proliferation .

(Idriss, Stull and Migden, 2024; Hoff *et al.*, 2009; Athar *et al.*, 2014).

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GLOSSARY FOR PAGE 18

- **Canonical pathway** – It is a process that has common features in an established or specific manner. However, when a new feature does not fit or partially fit in the established way is considered as non-canonical pathway (Biosynthesis, 2021)
- **Cell proliferation** – The increased growth/number of cells
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Protein** - A large molecule that is made of amino acids joined together.
- **Mutation** - A random change in the DNA that affects that particular gene or chromosome.
- **Transcription** - The process of using DNA as a template to make the single strand of nucleotide called ribonucleic acid (RNA).
- **Tumour suppressor** - A gene that encodes a protein to stop cancer growth.

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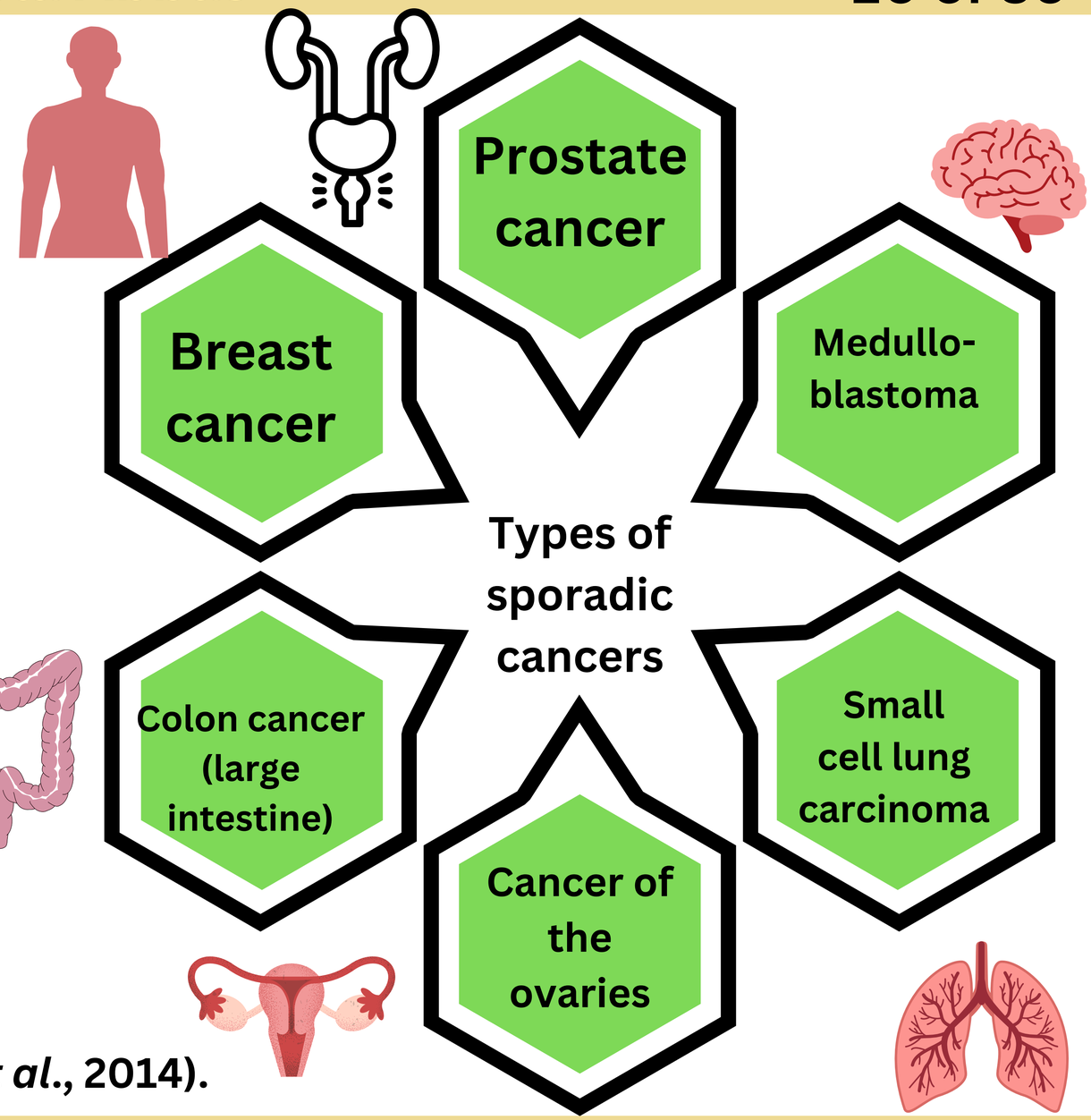
DYSREGULATED HEDGEHOG SIGNALLING PATHWAY

GLOSSARY

- **Medulloblastoma** - A form of brain cancer that arises in the cerebellum that functions in movement and balance. It is a malignant form that commonly occurs during childhood.
- **Small cell lung carcinoma** - small oval-shaped cancer cells with dark nuclei. It is found in the lungs commonly caused by smoking and can aggressively grow (National Cancer Institute, n.d).
- **Sporadic cancers** - They are are cancers that are neither hereditary nor have a family history that has mutated-gene caused cancer nor increased risk.



(Idriss, Stull and Migden, 2024; Hoff *et al*., 2009; Athar *et al*., 2014).

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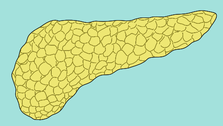
OTHER TYPES OF SPORADIC CANCER CAUSED BY DYSREGULATION OF HEDGEHOG SIGNALLING PATHWAY

Gastric cancer (Stomach)

Types of genes that encode Hedgehog signalling molecules namely, Single nucleotide polymorphism (SNP) and copy number polymorphism (CNP) for genetic screening.

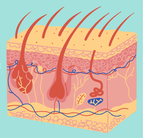
Pancreatic cancer

Hedgehog signalling switch hypoxia-induced cancer cells in the epithelial to mesenchymal transition which causes the cancer cells to invade the area.



Basal cell carcinoma (skin)

It is a global risk where there is 20-30% incidence (Cameron *et al.*, 2019). It has several risk factors including genetic syndromes e.g. Gorlin, Rombo and Bazex-Dupré-Christol syndromes (Goldenberg *et al.*, 2016). One of its main types is locally advanced BCC where overactivation of Sonic Hedgehof pathways can drive and cause it.



Brain cancer

Transcriptomic studies correlate between PTCH1 and GLI1 mRNA expression. The expression of GLI1 mRNA varied in the Glioblastoma patients (Carballo *et al.*, 2018).
Inflammatory cytokines, growth factors and proteins activate Hedgehog signalling pathway promoting glioblastoma cells (Shen *et al.*, 2024)

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GLOSSARY FOR PAGE 21

- **Cell** – The simplest unit of a living organism.
- **Copy number polymorphism** - Repeated sequences/patterns of genes. They vary in function - some have no defined roles whilst others experience change in shape, changes in metabolism nand increase risk of infection. and contribute to genetic syndromes or disorders.
- **Cytokines** – proteins that function in nonspecific and specific immune defenses providing chemical communication that synchronizes immune responses.
- **Epithelial–mesenchymal transition (EMT)** – single layer of cells (epithelial cells) have characteristics of mesenchymal cells (Manfioletti and Fedele, 2022). Mesenchymal cells are small cells that can differentiate into cells that produce connective tissue, for instance, osteoblasts (bone), preadipocytes (fat), fibroblasts, and chondroblasts (cartilage) (Sendic, 2023)
- **Gene** - A hereditary unit and a short section of DNA help determine the characteristics of an organism.
- **Glioblastoma** - An aggressive form of cancer that arises from non-nerve cells called glial cells in the brain
- **Single nucleotide polymorphism** - A difference in the DNA sequence caused by a single base. There are four bases found in DNA: Adenine Guanosine, Thymine and Cytosine.
- **Polymorphism** - the presence of two or more changes of a particular DNA sequence that vary from person to person
- **Transcriptomic** - It consists of a small percentage of the sequence that has been transcribed into RNA molecules. This is commonly less than 5% in humans. People can discover which genes are on or off in normal and cancer cells (Adams, 2008)

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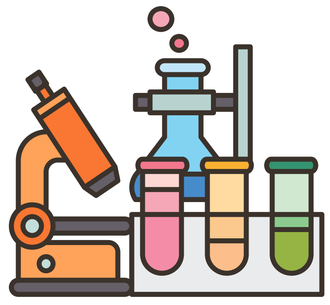
HEDGEHOG INHIBITORS

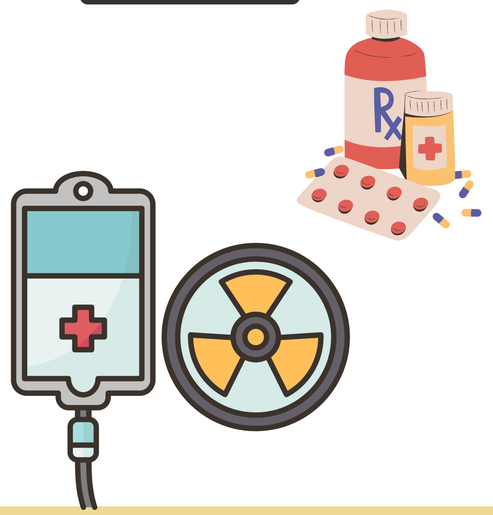
A small molecule (Robotnikinin) binds to the Hedgehog ligand – preventing its activation (Macarulla Mercade *et al*. 2024).
Effects: Disrupt tumour microenvironment and increase efficacy of chemotherapy.
Gli inhibitors prevent transcription induced by Gli (Macarulla Mercade *et a*l. 2024)



Advanced BCC are commonly prescribed Sonidegib and Vismodegib as first line of treatment (Niebel *et al*. 2020; Clinical Trials, 2024)

Other Hedgehog inhibitors investigated are:

- Patidegib (saridegib, IPI-926)
- Taladegib (LY2940680, ENV-101) - its an SMO antagonist (inhibits the function of SMO) in basal cell carcinoma which showed partial or complex response in 46.8% of patients at 10.2 months. The subsequent trial aims to study patients with refractory advanced solid tumors and Patched-1 loss-of-function mutations.
- Itraconazole: A medication used against fungi where it has also shown to suppress tumour growth by evading the Hedgehog signaling pathway and angiogenesis. (Farberg *et al.*, 2020; Deng *et al*. 2020)



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GLOSSARY FOR PAGE 23

- **Angiogenesis** - The production of new blood vessels for cells to receive the nutrients to function.
- **Chemotherapy** – Chemicals used to treat cancer
- **Ligand** - A signaling molecule that can commonly bind to a receptor or an enzyme.
- **Mutation** - A random change in the DNA that affects that particular gene or chromosome.
- **Refractory** – Not responsive or communicable.
- **Tumour microenvironment** - It is made of non-malignant cells (do not spread or are non-harmful) that interact with one another or with cancer cells. This can influence cancer progression and treatment response.

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RECENT DEVELOPMENT IN THERAPY

Recent studies discovered that inhibiting Smo proteins can promote tumour growth by evading Hedgehog signalling by activating the RAS/MAPK pathway (Mohan et al 2016).

Side effects are common with hedgehog inhibitors which lead to discontinuation e.g.:

- **Muscle spasms - fixed movement that is performed unwillingly/independently/involuntary**
- **Alopecia - loss of hair**
- **Weight Loss**
- **Dysguesia - loss a sense of taste**

One of the strategies to overcome the adverse effects in basal cell carcinoma is switching from vismodegib to sonidegib (± itraconazole) treatment (Di Raimondo *et al*. 2022).

Another strategy is through switching itraconazole to vismodegib (Zargari, Azimi and Geranmayeh, 2017)

The PD-1 inhibitor, Cemiplimab immunotherapy would be applied in patient cases where they could not tolerate hedgehog inhibitors. It was shown good safety and clinical efficacy but limited use to lower risk of tumour resistance and side effects (Idriss, Stull and Midgen, 2024)

GLOSSARY

Adverse events - Side effects that occur expectedly or unexpectedly in response to a medical event or pharmaceutical product.

Efficacys - Side effects that occur expectedly or unexpectedly in response to a medical event or pharmaceutical product.

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