REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

G Protein-Coupled Receptors: Chemical and Structural Insights for Drug Discovery

Manar I. Nagy [a], Safaa M. Kishk [a], Khaled M. Darwish [a], Samia Mostafa [a], Ismail Salama [a]*

[a] *Department of Pharmaceutical Medicinal Chemistry, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt*

Received: 13. 03. 2025

Revised: 15. 04. 2025

Accepted: 19. 04. 2025

*Correspondence Author:

Tel: +201007685893

E-mail address:

manar.nagy@pharm.suez.edu.eg

Abstract

G-protein coupled receptors (GPCRs) are very popular as integral membrane protein receptors which are used by cells to transfer the extracellular signals into intracellular responses. GPCRs form a superfamily which subdivided into 5 families [Glutamate (G), Rhodopsin (R), Adhesion (A), Frizzled/Taste2 (F), Secretin (S)] based on their phylogenetic tree. All subfamilies of GPCRs are made up of seven trans membrane proteins with three extracellular and three intracellular domains. Adenosine receptors are type of GPCRs. They are divided into four types of receptors (A_1R, A_2AR, A_2BR and A_3R). The accumulated extracellular adenosine mediates its regulatory functions by binding to one of four adenosine receptors. Adenosine emerges as a promising target for cancer therapy. It mediates protumor activities by inducing tumor cell proliferation, angiogenesis, chemo resistance, and migration/invasion by tumor cells. It also inhibits the functions of immune cells. In recent years, targeting one or more components of the adenosinergic pathway could be promising treatment strategies for individual cancer patients. The increasing evidence suggests that A_2AR and A_3R could be used as novel therapeutic targets for manipulating the antitumor immunity suppression.

Keywords: Cancer**,** GPCR, A_2AR,A_3R.

1. GPCR structures and families

GPCRs are integral membrane proteins which contain an extracellular amino terminus (N), seven trans-membrane α-helical domains and an intracellular carboxy terminus (C). Starting from the N-terminus, this protein winds up and down over the cell membrane, with the long middle segment traversing the membrane seven times in a serpentine pattern. The last part of the seven domains is tightly connected to the C-terminus. They respond to a various range of substances, including hormones, amines, lipids and neurotransmitters. (Schiöth & Fredriksson, 2005).

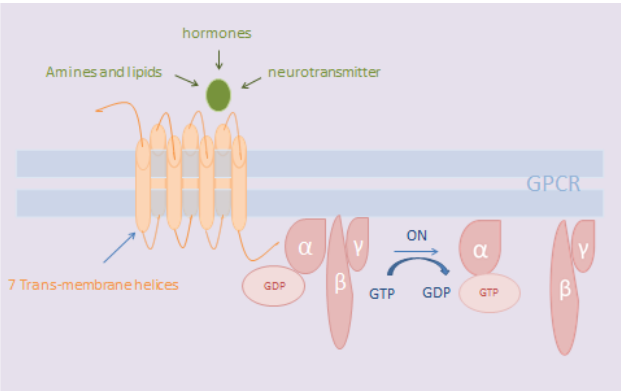

Fig.1: G-protein coupled receptor

There are various sorts of GPCRs, approximately 800 GPCRs which represent over 3% of human genes. GPCRs are categorized into different subfamilies based on physiological and structural features of the protein. The classification system, the A-F system, subdivides GPCRs into six classes, four of them contain mammalian GPCRs: class A Rhodopsin-like, that contains approximately 80% of GPCRs; class B Secretin-like; class C Metabotropic Glutamate Receptors; and class F Frizzled/Smoothened. The last two classes (class D and class E) are composed of non-mammalian GPCRs. The class D family are fungal mating pheromone receptors, and the class E family contains cAMP receptors from slime molds. (Schiöth & Fredriksson, 2005)

Recently, there is another classification system for the mammalian GPCRs. The GRAFS system subdivides mammalian GPCRs into 5 families [Glutamate (G), Rhodopsin (R), Adhesion (A), Frizzled/Taste2 (F), Secretin (S)] based on their phylogenetic tree. The common difference between the A-F and GRAFS system is that the last one separates the class B GPCR family into 2 different groups: the secretin family and the adhesion family. About 90% of all GPCRs are related to the rhodopsin family. (Schiöth & Fredriksson, 2005)

The demonstration of GPCRs was done in the 1970s by Robert J. Lefkowitz, the American physician and molecular biologist. Lefkowitz shared his 2012 Nobel Prize for Chemistry with his colleague Brian K. Kobilka, who helped him to elucidate GPCR function and structure. (Schiöth & Fredriksson, 2005)

2.GPCRs Signaling

GPCR protein expression, impaired ligand concentration, or mutation and signaling are involved in several patho-physiological conditions like cancer, central nervous system (CNS) disorders, metabolic and cardiovascular diseases, respiratory dysfunctions, gastrointestinal defects, eye defects, immune diseases and musculoskeletal diseases. So targeting of GPCRs is commonly used for therapeutic intervention; GPCRs are still the main targets for new drug development as it responds to approximetly 30% of the identified drug targets.(Schiöth & Fredriksson, 2005),(Aguinaga et al., 2019). Signal transduction started by a ligand-GPCR interaction on the cell surface level is the most prominent character of GPCRs. G proteins divide into two main functional units, an α subunit (Gα) and a βγ complex (Gβγ).The (Gα) subunit, a monomeric GTPase, has a main binding site for guanosine nucleotides. When (Gα) subunit binds to GDP, it becomes inactive, then attach to each other, and connect to GPCRs. Ligand binding to the receptors, which are also guanine nucleotide exchange factors (GEFs), activates the Gα subunit, stimulating the exchange of GDP for GTP as shown in fig.2.

This makes the G protein to detach away from the GPCR and the two units of G protein to dissociate. Each unit independently works on effector molecules to stimulate downstream signaling pathways. This signaling will continue until the Gα subunit hydrolyze the GTP molecule. Also, the signal is increased as the GPCR will continue to activate G proteins as long as the ligand is bound to the receptor. When the GTP is hydrolyzed to GDP, Gα-GDP returns to bind to the Gβγ dimer and the hetero trimeric G protein rebind to the GPCR.

GPCR signaling is complex, it leads to the start of a great diversity of downstream signaling pathways that regulate various cellular functions. This is due to different factors such as numerous receptor activation states, activation of non-G protein effector molecules, receptor dimerization and different subunit combinations for hetero trimeric G proteins exist because of the vast repertoire of Gα, Gβ, and Gγ isoforms. Each G protein subunit binds to certain GPCRs and have an effect on certain effector molecules.(Yang et al., 2021).

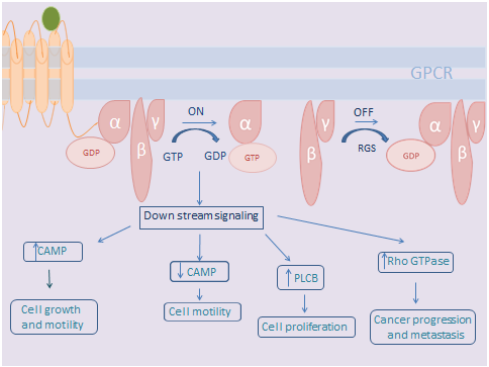

Fig.2: Signaling pathway of GPCR

The hydrolysis of the Gα-bound GTP molecule is the end of GPCR signaling. Although there is various mechanisms exist to regulate the GPCR signaling. Regulators of G Protein Signaling (RGS) is a various family of 20+ proteins which negatively control GPCR signaling. They interact with Gα subunits ($G\alpha_i$, $G\alpha_o$, and $G\alpha_z$) to accelerate GTP hydrolysis which lead to the end of signaling.

3. Physiological Functions of GPCRs

Since GPCRs are widely distributed and trigger cellular responses to a broad variety of extracellular stimuli, they play important roles in most physiological functions as sight, taste, smell, behavior, mood, immune system regulation, pheromone sensation, olfaction and light perception. Half of the 800 GPCRs mediate sensory information because more than 90% of them are expressed in the brain. They all involve certain extracellular signals which are converted into a cellular response.

For example, mood regulation is affected by GPCRs because these receptors in the mammalian brain can bind to different neurotransmitters and create different physiological responses. Dopamine, serotonin, and GABA are different molecules that can bind to GPCRs in the brain and lead to different moods .(A. Kumar & Plückthun, 2019).

3.1.GPCRs in Cancer

GPCRs are involved in different cancer types. They are expressed by tumor cells, as well as in many cells present in the tumor microenvironment including immune, stromal, and vascular cells. GPCRs and GPCR-mediated signaling regulate several cellular functions vital for cancer progression such as tumor cell proliferation, invasion, migration, and metastasis. Research has identified different GPCR signaling in several cancers due to aberrant overexpression, gain-of-function mutations, mutations in downstream effector molecules, and increased production of GPCR ligands by tumor and stromal cells.

3.1.1.The role of Adenosine receptors (GPCRs) in cancer

Adenosine receptors are type of GPCRs that comprise a group of glycoproteins with seven transmembrane domains, coupled to G proteins (Mazziotta et al., 2022). They are divided into four types of receptors (A_1R, A_2AR, A_2BR and A_3R). When adenosine binds to A_1R/A_3R, it causes a decrease in cAMP, while adenosine binding to A2AR and A_2BR causes an increase in cAMP.

Cancer development is associated with immunosuppressive tumor microenvironment (TME) which attenuates antitumor immune responses and promotes tumor cell immunologic escape. The conversion of extracellular ATP into adenosine by two cell-surface ectonucleosidases CD39 and CD73 play important roles in reshaping an immunosuppressive TME. The accumulated extracellular adenosine mediates its functions by binding to its adenosine receptors. Adenosine emerges as a promising target for cancer therapy. It mediates protumor activities by inducing tumor cell proliferation, angiogenesis, chemo resistance, and migration/invasion by tumor cells. It also inhibits the functions of immune cells, promoting the formation of a tumor-permissive immune microenvironment and favoring tumor escape from the host immune system. (Azambuja et al., 2019). Recently, targeting one of the components of the adenosinergic pathway could be apromising strategies for individual cancer patients, The increasing evidence suggests that A_2AR and A_3R could be used as novel therapeutic targets for manipulating the antitumor immunity suppression.

3.1.1.1. A_2AR

The human immune system is activated to fight against pathogens while inducing an array of mechanisms to protect against an excess inflammatory response or autoimmunity (Cekic & Linden, 2016). Unfortunately, these bypasses are sometimes hijacked by tumors, thus leading to immune evasion. These bypasses include inhibitory receptors such as PD-1, CTLA-4, TIM-3, and A_2AR, together with their related signaling networks, and are known as “immune checkpoint pathways” (V. Kumar, 2013), (Turcotte et al., 2015). Nowadays, the most promising cancer treatment is the blockage to one of this immune checkpoint pathways, which has revolutionized cancer therapy in the past 15 years. A_2A receptor, an emerging alternative immune checkpoint, have shown the potential to produce significant therapeutic effects. Physiologically, the extracellular level of adenosine is very low (Stagg et al., 2011). Pathologically, an elevated level of extracellular adenosine (~10 μM vs <1 μM in normal tissues) (Ryzhov et al., 2014) is specifically present in the TME and is available for tumor cells (Allard et al., 2014), Cancer-related fibroblasts (Thibaudin et al., 2016), and some immune cells, such as regulatory T cells (Tregs), Myeloid-derived suppressor cells (MDSCs), Endothelial cells (Ohta et al., 2006) and T helper cell 17 (Th17) (Kjaergaard et al., 2018). A2aR, among all four adenosine receptors, has the highest affinity for adenosine. Most immune cells express A2AR on the surface. As GPCR, A2AR on the surface of the

immune cell together with intracellular G_α (mainly

$G_{\alpha s}$ subunit) and G_{β}-G_{γ} form a complex. $G_{\alpha s}$ dissociated with G_{β}-G_{γ} after adenosine binding to A2AR and then undergo the GPCR signaling (Sun et al., 2022).

3.1.1.2. A_3R

Various studies have reported that A3 receptor (A_3R) is overexpressed in cancers. However, the role of A3AR in regulating cell proliferation and death is a relatively well debated issue, as this receptor acts in different way according to the tissue type in which it is expressed (A3R) (Rotondo et al., 2021). In certain tumors it promotes cell proliferation and survival, while in others tumors it triggers cytostatic and apoptotic pathways (Sitkovsky et al., 2014). A_3R stimulation inhibits lung cancer proliferation by arresting the cell cycle (Tumbarello & Turner, 2006). A similar effect observed in vitro in murine lymphoma (Gorzalczany & Sagi-Eisenberg, 2019). A_3R stimulation induces apoptosis in stomach cancer cells via a mechanism which involves PKC activation (Borea et al., 2018). An inhibition of tumor growth demonstrated also in lymphoma (Gorzalczany & Sagi-Eisenberg, 2019), leukemia (Klaasse et al., 2008), As well as colon and pancreatic carcinoma (Coppi et al., 2022). A_3AR stimulation prompts cell proliferation in other cancer types, such as colorectal cancer and adenocarcinoma (Fishman et al., 2004). This dual mode of action comprises the same signaling pathway. Based on this fact, A_3AR is having interest for its potential use as a therapeutic antitumor target (Hershfield & Seegmiller, 1977), (Pardoll, 2012).

3.2.GPCRs in the Nervous System

In the vertebrate nervous system, GPCRs are responsible for slow synaptic transmission, i.e., synaptic transmission which involves that activation of a series of biochemical events. Both the major excitatory and inhibitory neurotransmitters, glutamate and GABA respectively and a preponderance of other neurotransmitters,including acetylcholine, adenosin e, dopamine, serotonin, histamine, ATP, adrenaline/ noradrenaline, endocannabinoids, enkephalins/endo rphins, and neuropeptides, signal through GPCRS (Senese et al., 2020).

GPCRs located on the presynaptic membrane regulate the release of neurotransmitters while postsynaptic GPCRs can control gene expression and influence the efficiency of ionotropic receptors. Nervous system GPCRs play crucial roles in mood, cognition, pain, and appetite, and are involved in several neurodegenerative and psychiatric disorders.

3.3.GPCRs in the Immune System

GPCRs are expressed in many inflammatory cells, including dendritic cells, monocytes, lymphocytes, and neutrophils and play important roles in the immune system. Chemokine receptors are the signature GPCR subfamily associated with immune functions as they mediate the controlled migration of immune cells during innate and adaptive immunity (Lin et al., 2017).

Many other GPCR subfamilies, including adhesion GPCRs, purinergic receptors, adenosine receptors, formylpeptide receptors, and Lysophospholipid S1P and LPA receptors are important for immune responses as they regulate activities such as immune cell differentiation and maturation, phagocytosis and secretion of antimicrobial compounds. Aberrant GPCR expression or activation underlies the pathogenesis of many autoimmune diseases, immunodeficiencies, and autoinflammatory syndromes .

4. Pathophysiology

The loss or gain of GPCRs that caused by mutations responsible for more than 30 human diseases and syndromes . Mutational activation of GPCR (ie, constitutively activating mutations), such as mutations in an α1B-adrenergic receptor, specifically enhances receptor/G protein coupling in the absence of agonist ligands which could lead to cellular transformation and cancer.

Certain inherited diseases, such as *autosomal dominant non-autoimmune hyperthyroidism*, are caused by activating mutations in the TSH receptor gene. Similarly, a gain of function mutation in the *LHR* gene is known to cause a gonadotropin-releasing hormone (GnRH)-independent precocious puberty in boys, also called familial male-limited precocious puberty (FMPP) or testotoxicosis. *Jansen's metaphyseal chondrodysplasia* is a rare autosomal dominant form of short-limb dwarfism caused by activating mutations in the PTH/PTHrP receptor (Sente et al., 2018).

Loss of function of GPCRs due to amino acid

substitutions, truncations by nonsense or frame shift mutations, insertions, deletions, and rearrangements are also associated with many human diseases. For example, mutation of vasopressin V2 receptor (antidiuretic hormone receptor, AVPR2) and aquaporin 2 (AQP2) genes are linked to nephrogenic diabetes insipidus syndrome. Mutations in the Inactivating mutations in the rhodopsin (RHO) gene are the most common cause of retinitis pigmentosa (RP), which causes retinal dystrophy with early onset of night blindness and subsequent loss of the visual field (Sente et al., 2018).

Retinitis pigmentosa, is an eye disease in which the retina is damaged, caused by a mutation in a GPCR. This disease make the patient have blurred vision and/or difficulty seeing in low-light conditions, which is an inherited disorder with no treatment.

Wearing sunglasses can protect the remaining vision. There are over 800 different GPCRs in the human body. Mutations in different GPCRs would cause another conditions. Along with retinitis pigmentosa, recent studies have shown that mutations in these critical surface receptors can play a role in hypothyroidism, hyperthyroidism, nephrogenic diabetes insipidus, and fertility issues (Matúš & Prömel, 2018).

The G-protein itself can also be affected and need not be genetic. Cholera is caused by a bacteria that multiplies within the human intestine and secretes a protein called cholera toxin. This toxin penetrates the cells which line the intestine and modifies the G protein. The α subunit, which stimulates adenylyl cyclase, is the subunit modified. This modification prevents GTP hydrolysis and locks the G-protein in the active state. The constant stimulation of adenylyl cyclase results in a prolonged and excessive outflow of chloride ions and water into the gut. This leads to severe diarrhea and dehydration. This can quickly lead to death, so water and ions should be replenished as fast as possible. Treatment consists of rehydration and antibiotics (Matúš & Prömel, 2018).

Conclusion:

GPCRs are the largest class of membrane-bound receptors and one of the most prevalent gene families. These receptors are activated by various stimuli such as hormones, neurotransmitters, chemokines, odorants, and others. GPCRs influence broad physiological processes such as neurotransmission, cellular metabolism, secretion, cell growth, and immune responses. The availability of the structure of certain GPCRs has provided a basis for developing GPCR-based therapeutics.

However, detailed structural knowledge of most GPCRs is still lacking, which presents a significant challenge to target GPCRs for new therapeutics. GPCRs are widely expressed in human cells and tissues and crosstalk with other signaling pathways, such as receptor tyrosine kinases (RTKs) and ion channels. As a result, often, most drugs targeting GPCRs have unintended side effects. Finally, there are still many orphan GPCRs whose endogenous ligands and functions are not known.

References:

Aguinaga, D., Medrano, M., Cordomí, A., Jiménez-Rosés, M., Angelats, E., Casanovas, M., Vega-Quiroga, I., Canela, E. I., Petrovic, M., Gysling, K., Pardo, L., Franco, R., & Navarro, G. (2019). Cocaine Blocks Effects of Hunger Hormone, Ghrelin, Via Interaction with Neuronal Sigma-1 Receptors. Molecular Neurobiology, 56(2), 1196–1210. https://doi.org/10.1007/s12035-018-1140-7

Allard, B., Turcotte, M., Spring, K., Pommey, S., Royal, I., & Stagg, J. (2014). Anti-CD73 therapy impairs tumor angiogenesis. International Journal of Cancer, 134(6), 1466–1473. https://doi.org/10.1002/ijc.28456

Azambuja, J. H., Ludwig, N., Braganhol, E., & Whiteside, T. L. (2019). Inhibition of the adenosinergic pathway in cancer rejuvenates innate and adaptive immunity. International Journal of Molecular Sciences, 20(22). https://doi.org/10.3390/ijms20225698

Borea, P. A., Gessi, S., Merighi, S., Vincenzi, F., & Varani, K. (2018). Pharmacology of adenosine receptors: The state of the art. Physiological Reviews, 98(3), 1591–1625. https://doi.org/10.1152/physrev.00049.2017

Cekic, C., & Linden, J. (2016). Purinergic regulation of the immune system. Nature Reviews Immunology, 16(3), 177–192. https://doi.org/10.1038/nri.2016.4

Coppi, E., Cherchi, F., Venturini, M., Lucarini, E., Corradetti, R., Di Cesare Mannelli, L., Ghelardini, C., Pedata, F., & Pugliese, A. M. (2022).

Therapeutic Potential of Highly Selective A3 Adenosine Receptor Ligands in the Central and Peripheral Nervous System. Molecules, 27(6). https://doi.org/10.3390/molecules27061890

Fishman, P., Bar-Yehuda, S., Ohana, G., Barer, F., Ochaion, A., Erlanger, A., & Madi, L. (2004). An agonist to the A3 adenosine receptor inhibits colon carcinoma growth in mice via modulation of GSK-3β and NF-κB. Oncogene, 23(14), 2465–2471. https://doi.org/10.1038/sj.onc.1207355

Gorzalczany, Y., & Sagi-Eisenberg, R. (2019). Role of mast cell-derived adenosine in cancer. International Journal of Molecular Sciences, 20(10). https://doi.org/10.3390/ijms20102603

Hershfield, M. S., & Seegmiller, J. E. (1977). Coordinate regulation of the proximal and distal steps of the pathway of purine synthesis de nono in WI-L2 human lymphoblasts. Advances in Experimental Medicine and Biology, 76 A, 19–29. https://doi.org/10.1007/978-1-4613-4223-6_3

Kjaergaard, J., Hatfield, S., Jones, G., Ohta, A., & Sitkovsky, M. (2018). A2A Adenosine Receptor Gene Deletion or Synthetic A2A Antagonist Liberate Tumor-Reactive CD8+ T Cells from Tumor-Induced Immunosuppression. The Journal of Immunology, 201(2), 782–791. https://doi.org/10.4049/jimmunol.1700850

Klaasse, E. C., IJzerman, A. P., de Grip, W. J., & Beukers, M. W. (2008). Internalization and desensitization of adenosine receptors. Purinergic Signalling, 4(1), 21–37. https://doi.org/10.1007/s11302-007-9086-7

Kumar, A., & Plückthun, A. (2019). In vivo assembly and large-scale purification of a GPCR - Gα fusion with Gβγ, and characterization of the active complex. PLoS ONE, 14(1), 1–25. https://doi.org/10.1371/journal.pone.0210131

Kumar, V. (2013). Adenosine as an endogenous immunoregulator in cancer pathogenesis: Where to go? Purinergic Signalling, 9(2), 145–165. https://doi.org/10.1007/s11302-012-9349-9

Lin, H., Hsiao, C., & Pabst, C. (2017). Adhesion GPCRs in Regulating Immune Responses and Inflammation. 136, 163–201. https://doi.org/10.1016/bs.ai.2017.05.005

Matúš, D., & Prömel, S. (2018). G proteins and GPCRs in C. elegans development: A story of mutual infidelity. Journal of Developmental Biology, 6(4), 1–18. https://doi.org/10.3390/jdb6040028

Mazziotta, C., Rotondo, J. C., Lanzillotti, C., Campione, G., Martini, F., & Tognon, M. (2022). Cancer biology and molecular genetics of A3 adenosine receptor. Oncogene, 41(3), 301–308. https://doi.org/10.1038/s41388-021-02090-z

Ohta, A., Gorelik, E., Prasad, S. J., Ronchese, F., Lukashev, D., Wong, M. K. K., Huang, X., Caldwell, S., Liu, K., Smith, P., Chen, J. F., Jackson, E. K., Apasov, S., Abrams, S., & Sitkovsky, M. (2006). A2A adenosine receptor protects tumors from antitumor T cells. Proceedings of the National Academy of Sciences of the United States of America, 103(35), 13132–13137. https://doi.org/10.1073/pnas.0605251103

Pardoll, D. M. (2012). The blockade of immune checkpoints in cancer immunotherapy. Nature Reviews Cancer, 12(4), 252–264. https://doi.org/10.1038/nrc3239

Rotondo, J. C., Lanzillotti, C., Mazziotta, C., Tognon, M., & Martini, F. (2021). Epigenetics of Male Infertility: The Role of DNA Methylation. Frontiers in Cell and Developmental Biology, 9(July). https://doi.org/10.3389/fcell.2021.689624

Ryzhov, S. V., Pickup, M. W., Chytil, A., Gorska, A. E., Zhang, Q., Owens, P., Feoktistov, I., Moses, H. L., & Novitskiy, S. V. (2014). Role of TGF-β Signaling in Generation of CD39+CD73+ Myeloid Cells in Tumors. The Journal of Immunology, 193(6), 3155–3164. https://doi.org/10.4049/jimmunol.1400578

Schiöth, H. B., & Fredriksson, R. (2005). The GRAFS classification system of G-protein coupled receptors in comparative perspective. General and Comparative Endocrinology, 142(1-2 SPEC. ISS.), 94–101. https://doi.org/10.1016/j.ygcen.2004.12.018

Senese, N. B., Kandasamy, R., Kochan, K. E., & Traynor, J. R. (2020). Regulator of G-Protein Signaling (RGS) Protein Modulation of Opioid Receptor Signaling as a Potential Target for Pain Management. Frontiers in Molecular Neuroscience, 13(January), 1–11. https://doi.org/10.3389/fnmol.2020.00005

Sente, A., Peer, R., Srivastava, A., Baidya, M., Lesk, A. M., Balaji, S., Shukla, A. K., Babu, M. M., & Flock, T. (2018). Molecular mechanism of modulating arrestin conformation by GPCR

phosphorylation. Nature Structural & Molecular Biology. https://doi.org/10.1038/s41594-018-0071-3

Sitkovsky, M. V., Hatfield, S., Abbott, R., Belikoff, B., Lukashev, D., & Ohta, A. (2014). Hostile, hypoxia-A2-adenosinergic tumor biology as the next barrier to overcome for tumor immunologists. Cancer Immunology Research, 2(7), 598–605. https://doi.org/10.1158/2326-6066.CIR-14-0075

Stagg, J., Divisekera, U., Duret, H., Sparwasser, T., Teng, M. W. L., Darcy, P. K., & Smyth, M. J. (2011). CD73-deficient mice have increased antitumor immunity and are resistant to experimental metastasis. Cancer Research, 71(8), 2892–2900. https://doi.org/10.1158/0008-5472.CAN-10-4246

Sun, C., Wang, B., & Hao, S. (2022). Adenosine-A2A Receptor Pathway in Cancer Immunotherapy. Frontiers in Immunology, 13(March), 1–9. https://doi.org/10.3389/fimmu.2022.837230

Thibaudin, M., Chaix, M., Boidot, R., Végran, F., Derangère, V., Limagne, E., Berger, H., Ladoire, S., Apetoh, L., & Ghiringhelli, F. (2016). Human ectonucleotidase-expressing CD25high Th17 cells accumulate in breast cancer tumors and exert immunosuppressive functions. OncoImmunology, 5(1). https://doi.org/10.1080/2162402X.2015.1055444

Tumbarello, D. A., & Turner, C. E. (2006). Hic-5 Contributes to Transformation Through a RhoA / ROCK-dependent Pathway. Journal Cellular Physiology, 211(3)(May), 736–747. https://doi.org/10.1002/JCP

Turcotte, M., Spring, K., Pommey, S., Chouinard, G., Cousineau, I., George, J., Chen, G. M., Gendoo, D. M. A., Haibe-Kains, B., Karn, T., Rahimi, K., Le Page, C., Provencher, D., Mes-Masson, A. M., & Stagg, J. (2015). CD73 is associated with poor prognosis in high-grade serous ovarian cancer. Cancer Research, 75(21), 4494–4503. https://doi.org/10.1158/0008-5472.CAN-14-3569

Yang, D., Zhou, Q., Labroska, V., Qin, S., Darbalaei, S., Wu, Y., Yuliantie, E., Xie, L., Tao, H., Cheng, J., Liu, Q., Zhao, S., Shui, W., Jiang, Y., & Wang, M. W. (2021). G protein-coupled receptors: structure- and function-based drug discovery. Signal Transduction and Targeted Therapy, 6(1). https://doi.org/10.1038/s41392-020-00435-w