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Role of G-Protein Coupled Receptors in Cancer Research and Drug Discovery

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ABSTRACT

G-Protein Coupled Receptors as the largest class of cell surface signaling proteins are widely considered in drug discovery programs as therapeutic drug targets; their contribution in drug discovery process is because of their critical role in many physiological functions and their link with emerging different types of diseases including cancer development and cancer metastasis. Their association to hereditary diseases, made them important for examination as novel targets too. As they constitute the target of 50% of the available therapeutic agents in the market, they are still most attractive potential targets for developing new drugs especially anti-cancer drugs. Their structure –function relationship have been made them a powerful basis for screening a large number of pharmaceutical products. In this paper we purpose to review significant role of the GPCRs in cancer development and drug discovery along with the information regarding their structure, classification and recent studies and findings about their position as drug targets. This review provides scientists for development of favorable opportunities for drug discovery in cancer research including prevention and diagnosis and treatment.

Keywords: Corporation of G-Protein Coupled Receptors, Drug Target, Drug Discovery, Associated Disesaeas, Cancer

I. INTRODUCTION

G-Protein Coupled Receptors are the largest class of cell surface signaling proteins which form the biggest class of drug targets. Their physiological functions and their link with emerging different types of diseases especially development of cancers and metastasis, have been made them significant for drug discovery programs and hiring them as therapeutic drug targets. In this paper we first focus on their structure, classification, mechanism of peptide and non-peptide interactions then discuss their role in drug discovery and recent finding related to their position as novel drug targets in drug discovery. [1,2].The purpose of this review is to redefine the structure-function relationship of the CPCRs as a valuable source for development of novel drugs and provide favorable and tremendous opportunities in prevention and treatment of cancers. Mechanism of their activation is carried out through ligand binding to a G-protein, which in turn activates or inactivates an enzyme that produces a specific second messenger or induces modulation of an ion channel, results in an alternation in membrane potential. Examples for GPCRs are the receptors for calcitonin, glucagon, serotonin, epinephrine, etc. The CPCRs consisting of seven hydrophobic regions that constitute membrane stretching alpha helices, joined by intracellular and extracellular loops. The intracellular loops constitute the heterotrimeric G-protein binding domains and include three subunits: the alpha subunit (35 kDa) family, the beta subunit (35-36 kDa) family and the gamma subunit(6-10kDa) family. After ligand –receptor binding, the heterotrimeric G-proteins detach into two activated subunits: Gα GTP and Gβγ.The ligand binding stimulus conformational change of the receptor, which leads to alternation of the Gα, decreases the affinity for GDP,

which is replaced by GTP. The Galpha CTP conformation has a decreased affinity for G beta gamma, results in dissociation of subunits from each other and the receptor. Activation of effectors is carried out by Gα GTP and free Gβγ. The hydrolysis of GTP is carried out by its intrinsic GTPase activity. Moreover, acceleration the intrinsic GTPase activity of Gα is aided by regulatory proteins (RGS proteins). This signaling route is deactivated during hydrolysis of GTP to GDP by Gα which subsequently binds free Gβγ to form an inactive heterotrimer which may be bound to a GPCR. This mechanism of signaling serves as a switch that can turn on and off signaling routs. GPCRs are classified into three distinct groups : Class A: Rhodesian-like-receptors which form the biggest class of GPCRs including receptors for Rhodesian and adrenaline and most other 7 transmembrane receptor types such as olfactory subclass. Class B: This class consists of approximately 25 membranes, including receptors for corticotropic releasing hormones, calcitonin hormones, parathyroid hormone, growth hormone releasing hormone and gastrointestinal peptide hormone family like secretin, VIP, glucagon.The activation of the receptors of this class is carried out by large peptide including high amino acid identity. Class C: This group is the smallest group of GPCRs and contains calcium sensing receptors and metabotropic glutamate. The prominent characterization of this class is a large N terminal domain with specific motifs containing the proper neurotransmitter or hormone binding sites. Mechanism of G-protein binding is done through the following stages: first the activation of the receptor is carried out by the ligand (agonist), secondly, Binding G-protein to the activated receptor is occurred, during G-protein coupling progression, ligand binding to the receptor become stronger. Then the release of GDP occurred-protein picks GTP up, GTP triggers the dissociation of G-protein from the receptor. Mechanism of peptide interaction is as follow: First binding of C-terminal of the peptide and N-domain of the receptors occurred, subsequently, binding of the N-terminal of the ligand to the J-domain occurred which leads in activation the receptors results in stimulation of intracellular signaling.Non-peptide interaction with class B is as follow: first of all, binding of the non –peptide antagonist to the J-domain occurred leads to formation of antagonist-receptor complex while the peptide ligand is free. In this interaction, a change in the J-domain occurred, inhibiting peptide binding to the J-domain, subsequently, the interaction between the peptide-J-domain is blocked so that the receptor signaling is blocked by the non-peptide antagonist, this is because of prevention of G-protein activation.One conclusion is obtained from non-peptide interaction which is allosteric modulation of the GPCRs. This deduction suggests the significant role of the GPCRS in drug discovery as drug target using their modulation. [1-5].

II. METHODS AND MATERIAL

Role of the GPCRs in cancer research and drug discovery:

In the previous section, we mentioned the role and importance of the GPCRs in drug discovery as therapeutic drug target. Among classes of GPCRs, class B are largely participated in major pathophysiological and biological functions, hence they have verified to be a big opportunity for designation of novel drugs. Their functions made them stimulus for drug discovery programs and also supported the studies performed using GPCR knockout animals. In this section, for better understanding the role and participation of GPCRs in drug discovery we discussed some recent discoveries about their selection as drug target in drug discovery programs. Recently, scientist worked on discovery of novel therapeutic targets and prognostic factors in head and neck squamous cell carcinoma (HNSCC).They succeeded with identification of several G protein-coupled receptors (GPCRs) as potential candidates. They have observed the occurrence of important epigenetic silencing of GPCR expression as compared to healthy tissue which showed significant correlation with clinical behavior.Additionally, they have observed the suppression tumour cell growth by GPCR activity which together indicates potential utilization of the GPCR expression as a prognostic factor. In the previous studies some receptors identified in association with HNSCC such as *galanin receptor type 1 (GALR1)* which function in inhibition of HNSCC cells though ERK1/2-mediated effects on proteins controlling cell cycles such as p27, p57, and cyclin D1, *type 2 (GALR2),* its role is indicated by its inhibition of activity for cell proliferation and induction of apoptosis in HNSCC cell, *tachykinin receptor type 1 (TACR1*)and *somatostatin receptor type 1 (SST1)* which both are in association with significantly decreased diseases –free survival and a higher frequency rate. Their studies demonstrated the

potential utility of the GPCRs in HNSCC research as its use as therapeutic drug target.[6].In another approach, scientists understood the role of G-protein estrogen receptor (GPER) in breast cancerous cells and cancer associated fibroblasts(CAFs).In this study, they have demonstrated binding of nicotinic acid and nicotinamide to the GPER-mediated signalling pathway results in its activation and played important role in breast cells and CAFs. Both of nicotinic acid and nicotinamide were able to promote the up-regulation of GPER target genes via the EGFR/ERK transduction pathway. Their studies support the supplementary role of the two molecules (nicotinic acid and nicotinamide) in induction of proliferation and migration of cancerous cells in breast and CAFs via GPCR-dependent route.Theri study supported significant role of GPCR as therapeutic drug target [7].Another interesting research on GPCRs has shown their significant role in cancer development via GPCR-CARMA3-NF-κB signaling axis which is appearing as a new therapeutic drug target for cancer research. In this signaling route, activation of NF-κB is carried out by GPCR and abnormal regulation of GPCR-NF-κB signalling axis leads to cancer development. However, it has been shown that a new scaffold protein named CARMA3 is crucial in activation of GPCR-NF-κB signalling axis, so GPCR-CARMA3-NF-κB signalling axis forms a opportunity for drug discovery for treatment and control of diseases. [8].The role of GPCRs in development of colon carcinogenesis has been evaluated. In one if related study, scientists investigated the increased gene expression of G protein–coupled receptor 48 (GPR48) in the $p27^{+/-}$ cells which form cyclin-dependent kinase inhibitor involved in increased tumor malignancy and weak prognosis in HCT116 human colon carcinogenesis. They have also showed the participation of GPR48 in lung carcinoma and lymph node metastasis. So this potential prognostic factor can be utilized in cancer research and drug discovery as a therapeutic target. [9].Scientists have examined the expression of 929 GPCR transcripts in tissue samples of squamous cell cancer (10 patients) and adenocarcinoma (7 patients) for identification of novel targets for treatment of non-small cell lung carcinoma (NSCLC).As a result, they have identified 5 significantly increased expressed GPCRs associated in squamous cell carcinoma.These five GPCRs are arranged in descending order of expression as follow: GPR87 > CMKOR1 > FZD10 > LGR4 > P2RY11. Out of which, LGR4 and CMKOR1 are orphan receptors and GPR87 has shown potential utilization in drug discovery as a target validation because of its prominent overexpression and link with squamous carcinoma. [10].In another studies, the role of orphan G-protein–coupled receptor, *Gpr49* in human hepatocellular carcinomas and GPR56 in tumor adhesion evaluated which demonstrated the prominent role of GPCRs family in cancer development and their utilization as valid candidate for target validation [11,12].Recent studies demonstrated that over-expression of some genes encoding GPCR-PCa, PSGR2, CaSR, GPR30, and GPR39 [13]. were linked with carcinogenesis and metastasis in various type of cancers.GPCR-PCa and PSGR2 associated in human prostate cancer [14,15] CaSR associated with breast cancer cells evolved from bone metastases [16,17].GPR30 is in association with breast cancer cells and induces proliferation and migration of them via connective tissue growth factor[18,19]. GPR39 is involved in lymph node metastasis and advanced TNM stage [20]. Additionally, many GPCR ligands such as phingosine-1-phosphate [21]. LPA [22-24], thrombin [25]. platelet-activating factor [26,27], interleukin-8 [28], monocyte chemoattractant protein 1 [29],growth regulated oncogene α-γ [13],and stromal cell-derived factor have also been observed and examined for their participation in vasculogenesis, tumor-induced angiogenesis, tumour growth and metastasis [30]. These findings have been helped in providing new strategies for cancer control including prevention, diagnosis and treatment.

III. CONCLUSION

The GPCR family as the largest cell-surface proteins in mammalian genomes are physiologically and biologically very important and any disturbance in their function and genes are associated with development of various types of diseases. Among the associated diseases, development of various types of cancers such as breast, prostate, head and neck squamous cell carcinoma (HNSCC), colon cancer, squamous cell carcinoma (SCC) of the lung, hepatocellular carcinoma, basal cell carcinoma (BCC) and lymph node metastasis are investigated well. The GPCRs family have shown potential utility as therapeutic target in cancer research studies and control. Although GPCRs introduced as a significant target group for various type of cancer in for pharmaceutical therapeutics, some limitations are visible

in their role as potential drug targets which is mainly is due to problems in the identification of their natural ligands. Although high-throughput screening technologies effectively has been solved these difficulties but due to multiple roles and associations of GPCRs in cancer prevention, diagnosis and treatment, have been demanded more precise and integrative system biology approaches for unrevealing biological mechanism of cancers and to decrease limitations are present in diagnosis and drug development for cancerous diseases. Recently for rapid and precise cancer control, multidisciplinary approaches such as Bioinformatics. Biotechnology, engineering and medicine and biology disciplines related to physics have been utilized together for understanding the dynamic networks of GPCRs interactions within a cell.The need for development of new technologies and new systems biology approaches for identification, study and analysis of GPCRs in the cancers are urgent. The newly developed sciences such as bioinformatics with cooperation mathematics helped in revealing signaling networks linked with GPCRs. The new technologies help in revealing abnormal regulation of GPCRs associated signaling axes.We hope in near future effective and complementary technologies will be developed for cancer control programs depend on GPCRs associations. At the end We have to add this point, although there are various cell surface drug targets such as ion channels, [31], Cyclin independent kinases (CDKs)[32], Aquaporins [33]and so on which have been shown successful results in cancer diagnosis, prevention and treatment, but GPCRs as they have formed the largest drug targets marketed so far, they deserve the most important attention in drug discovery programs.

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