

# HISTAMINE RECEPTORS AND CANCER PHARMACOLOGY: AN UPDATE

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## ABSTRACT

In the present review we will discuss the recent advances in the understanding of the role of histamine and histamine receptors in cancer biology. The controversial role of the histaminergic system in different neoplasias including gastric, colorectal, oesophageal, oral, pancreatic, liver, lung, skin, blood and breast cancers will be reviewed. The expression of histamine receptor subtypes, with special emphasis in histamine H4 receptor (H4R), in different cell lines and human tumours, the signal transduction pathways and the associated biological responses as well as the *in vivo* treatment of experimental tumours with pharmacological ligands will be described. The presented evidence demonstrates that histamine regulates cancer-associated biological processes during cancer development in multiple cell types, including neoplastic cells and cells of tumour microenvironment. The outcome will depend on tumour cell type, histamine receptors expression, signal transduction associated to those receptors, tumour microenvironment and histamine metabolism, supporting the complexity of cancer disease. Findings show the pivotal role of H4R in the development and progression of many types of cancers, and considering its immunomodulatory properties, H4R arises as the most promising molecular therapeutic target for cancer treatment within histamine receptor family. Furthermore, H4R is differentially expressed in tumours compared with normal tissues and in most cancer types in which data was available, H4R expression is associated to clinicopathological characteristics, suggesting that H4R might represent a novel cancer biomarker.

**KEYWORDS:** histamine H4 receptor, breast cancer, gastrointestinal cancer, melanoma, leukaemia, lung cancer, anticancer treatment

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**ABBREVIATIONS:** ALL, acute lymphocytic leukaemia; AML, acute myeloid leukaemia; AOM azoxymethane; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma extra-large; BNCT, boron neutron capture therapy; bw, body weight; CCA, Cholangiocarcinoma; Cdc, cell division cycle; CDK, cyclin-dependent kinase; CML, acute myeloid leukaemia; CNS, central nervous system; COX-2, cyclooxygenase; CRC, colorectal cancer; CRE, cAMP responsive elements; DAG, 1, 2-diacylglycerol; DAO, diamine oxidase; DPH, diphenhydramine; DSS, dextran sodium sulphate; ECL, human enterochromaffin-like cells; ECM, extracellular matrix; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ER, oestrogen receptor; ERK1/ERK2, extracellular signal-regulated kinases (ERK1/2); ESCC, oesophageal squamous cell carcinoma; ETM, epithelial to mesenchymal transition; Ets-1, v-ets erythroblastosis virus E26 oncogene homolog; FBLN5, matrix protein fibulin-5; GC, Gastric carcinoma; GI, Gastro-intestinal; GRK2, G protein-coupled receptor kinase 2; HCC, hepatocellular carcinoma; HD, Hodgkin's disease; HDC, L-histidine decarboxylase; HER 2, human epidermal growth factor 2 receptor; H4R, histamine H4 receptor; H4R-KO, H4R knockout; HNMT, histamine N-methyltransferase; HNSCC, head and neck squamous cell carcinoma; H3R, histamine H3 receptor; H1R, histamine H1 receptor; H2R, histamine H2 receptor; IBS, irritable bowel syndrome; IL, Interleukin; IFN $\alpha$ , interferon-alpha; IFN $\gamma$ , interferon-gamma; IGF-IIR, insulin-like growth factor II receptor; ip, intraperitoneal; KO, knockout; LLC, Lewis lung carcinoma; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; MDSC, myeloid derived suppressor cells; MRPs, multidrug resistance-associated proteins; NOX-2, NADPH oxidase 2; NHL, non-Hodgkin lymphomas; NK, natural killer; NMU, N-nitro-N-methylurea; NSCLC, Non-small cell lung cancer; ODC, Ornithine decarboxylase; OSCC, oral squamous cell carcinoma; OS, overall survival; OTSCC, oral tongue squamous cell carcinoma; PCNA,

proliferating cell nuclear antigen; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species; sc, subcutaneous; TCGA, The Cancer Genome Atlas; TDLN, tumour draining lymph nodes; TGF $\beta$ , transforming growth factor-beta; TILs, tumour infiltrating lymphocytes; TNBC, triple negative breast cancers; TNF $\alpha$ , tumour necrosis factor-alpha; TNM, tumour-nodes-metastasis; tpm, transcripts per million; Tregs, regulatory T cells; VEGF, vascular endothelial growth factor

## INTRODUCTION

Cancer is a main public health concern, representing a leading cause of death in both more and less economically developed countries (Ferlay *et al.*, 2015; Torre *et al.*, 2015). Although advances in cancer research over the last decades lead to novel and improved anti-neoplastic drugs, anticancer therapy continues to have detrimental outcomes, including both poor response and severe toxicity. To overcome the complexity of the oncological disease, future anti-cancer treatments should target the different cellular and molecular participants encompassed in a tumour and its microenvironment, as well as their specific interactions to increase therapeutic efficacy.

Cell proliferation is critical for tumour development and progression, and histamine is a main mediator of this biological process in different types of cancers (Medina and Rivera, 2010). Histamine [2-(4-imidazolyl)-ethylamine] is an endogenous biogenic amine widely distributed throughout the body and it is involved in numerous physio-pathological conditions. Histamine performs its functions via four histamine receptors subtypes that belong to the family of G protein coupled receptors (Panula *et al.*, 2015). The H1 receptor (H1R) was the first receptor subtype to be discovered and to be targeted for clinical use, as its antagonists are used for the treatment of allergic inflammation. H1R is a G $\alpha$ q/11-coupled

protein, which stimulates phospholipase C (PLC) to generate inositol 1, 4, 5-triphosphate and 1, 2-diacylglycerol (DAG) leading to an increase in cytosolic  $\text{Ca}^{2+}$ . In addition, cAMP accumulation is stimulated via  $\text{G}\beta\gamma$  subunits of  $\text{G}_q$  (Hill *et al.*, 1997; Panula *et al.*, 2015).

Histamine H2 receptor (H2R) was the second histamine receptor subtype discovered. Numerous H2R antagonists are clinically used to block histamine-induced gastric acid secretion. H2R is both coupled to adenylate cyclase and to phosphoinositide second messenger systems via separate GTP-dependent mechanisms. Several studies have shown that histamine induced H2R-dependent effects were predominantly mediated through the accumulation of cAMP in various cells (Johnson, 1982; Dy *et al.*, 2004; Panula *et al.*, 2015). The third histamine receptor was reported in 1983 by a traditional pharmacological approach.

Histamine H3 receptor (H3R) belongs to the G-protein-coupled receptors ( $\text{G}_{ai/o}$ ) and its activation leads to inhibition of cAMP formation, accumulation of  $\text{Ca}^{2+}$  and stimulation of mitogen-activated protein kinase (MAPK) pathway (Dimitriadou *et al.*, 1994; Shahid *et al.*, 2009). *HRH3* gene counts with three introns, showing significant splice variance (Shahid *et al.*, 2009) and H3R blocking ligands are in the search for the treatment of central nervous system (CNS) disorders (Kantor, 2006; Dauvelliers *et al.*, 2013; Kasteleijn-Nolst *et al.*, 2013; Amini, *et al.*, 2015; Szakacs *et al.*, 2017).

Histamine H4 receptor (H4R) is the latest histamine receptor described of this family. H4R is a  $\text{G}_{ai/o}$  coupled receptor, and its agonists-induced stimulation leads to an inhibition of adenylyl cyclase (AC) and downstream cAMP responsive elements (CRE) as well as activation of MAPK and PLC with calcium mobilization (Shahid *et al.*, 2009; Panula *et al.*, 2015). The main characteristics of histamine receptors and compounds used in their investigation are summarised in Table 1. Approved antagonists of all histamine receptors are used clinically (Panula *et al.*, 2015) and the recent data from ongoing clinical trials are

described in Table 2. It is important to highlight that all four histamine receptors are identified in several human tumours.

The purpose of this review is to address the most recent research on the involvement of histamine and histamine receptors in the complex cancer biology, considering tumour cells and the interaction with their microenvironment, emphasizing the remarkable role of the latest histamine receptor subtype, the H4 receptor (H4R). Presented data contribute to the identification of potential molecular targets for effective anti-cancer therapies.

### **Histamine receptors and gastrointestinal cancers**

Gastro-intestinal (GI) cancer is one of the most common forms of neoplasia and refers to a group of cancers that affects the digestive system organs, including oesophagus, gallbladder, liver, pancreas, stomach, small intestine, colon and rectum (Torre *et al.*, 2015).

Histamine producing cells and the four histamine receptors subtypes are widely distributed throughout the digestive system. Histamine is involved in several physiological responses such as vascular contraction and permeability, parietal cell acid secretion, gastric mucosal defence and immune modulation through the H1R, H2R, H3R and H4R, respectively (Bertaccini & Coruzzi, 1992; Coruzzi *et al.*, 2012; Deiteren *et al.*, 2015). In addition, histamine and its receptors are involved in GI disorders, such as allergic enteropathy, inflammatory bowel disease, irritable bowel syndrome (IBS) and cancer (Chandra & Ganguly, 1987; Reynolds *et al.*, 1997; Masini *et al.*, 2005; Coruzzi *et al.*, 2012; Kennedy *et al.*, 2012). In this section we will review the most relevant data of the functional role of histamine receptors in GI cancers.



## Histamine receptors and colorectal cancer

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, with extensive geographical variation in incidence and mortality (Ferlay *et al.*, 2015; Torre *et al.*, 2015; Pilleron *et al.*, 2018).

Rectal cancers, which account for one-third of CRCs, have particular biological hallmarks (Tamas *et al.*, 2015). Surgery remains the mainstay of treatment for colon cancer but use of laparoscopic approaches varies widely despite demonstrated short- and long-term benefits (Ratnapradipa *et al.*, 2017). Immunotherapy is a novel promising approach for CRC (Gutting *et al.*, 2018).

Both high activity of L-histidine decarboxylase (HDC) and low activity of histamine catabolizing enzymes are observed in carcinoma or adenoma compared to normal mucosa, supporting the hypothesis that histamine could be involved in colon carcinogenesis (Reynolds *et al.*, 1997; Garcia-Caballero *et al.*, 1988; Cianchi *et al.*, 2005; Kuefner *et al.*, 2008). However, determination of histamine levels in whole blood of CRC patients indicates a significant histamine reduction when compared to controls (Burtin *et al.*, 1983; Previati *et al.*, 2002).

CRC patients with lymph node invasion had a particularly higher density of HDC-positive microvessels and show high proliferative activity. These results suggest that apart from mast cells, vessels could be additional sources of histamine, which may promote angiogenesis in human CRC (Cui *et al.*, 2013). On the other hand, it is important to highlight that chemically induced carcinogenesis developed in HDC knockout (KO) mice shows enhanced inflammation and higher tumour burden (intestine and skin) compared to wild type animals. These effects were reversed by histamine administration (Yang *et al.*, 2011). In addition, histamine-producing probiotic (hdc+ *Lactobacillus reuteri*) decreased the number and size of

colon tumours, reducing the gene expression of proinflammatory cancer-associated cytokines (keratinocyte chemoattractant, interleukin (IL)-22, IL-6, tumour necrosis factor (TNF), and IL-1 $\alpha$  gene expression) in the colonic mucosa and reduced the amounts of proinflammatory mediators, cancer-associated cytokines, keratinocyte chemoattractant, IL-22 and IL-6 in plasma, indicating that histamine suppresses colorectal tumorigenesis and severity of inflammation-associated colon cancer in HDC KO mice. Histamine-generating *L. reuteri* also decreased the relative numbers of splenic CD11b+Gr-1+ immature myeloid cells. Furthermore, an isogenic HDC-deficient *L. reuteri* mutant that was unable to generate histamine did not suppress carcinogenesis, indicating a significant role of the cometabolite, histamine, in suppression of chronic intestinal inflammation and colorectal tumorigenesis. In this connection, elevated HDC gene expression is associated with improved survival outcomes in CRC patients (Gao *et al.*, 2017). Moreover, it was demonstrated the immunohistochemical expression of H1R, H2R, H3R and H4R in adenocarcinoma cells (Tanaka *et al.*, 2016a) and that all histamine receptor subtypes are involved in cancer (Kennedy *et al.*, 2012).

Loratadine effectively inhibited growth of tumours derived from human colon cancer cells (COLO 205) *in vivo*. *In vitro* studies demonstrated that this H1R antagonist induced a cell division cycle (Cdc) 2-associated G2/M cell cycle arrest and apoptosis by interfering with the activity of regulatory proteins involved in cell cycle progression, more precisely, with checkpoint kinase 1-mediated phosphorylation of Cdc25C signalling (Chen *et al.*, 2006). In addition, treatment with loratadine inhibited growth and enhanced the effect of radiation of human CRC cell lines. According to the results presented, H1R signalling could interfere with ionising radiation at different levels, enhancing DNA damage and activating Chk1 and therefore inducing G2/M arrest, the most radiosensitive phase associated to increase in radiation-induced DNA damage (Soule *et al.*, 2010).

In line with these results, it was shown that the H1R antagonist meclizine, dose-dependently induced apoptosis in human colon cancer cell lines (COLO 205 and HT 29 cells), down regulating Bcl-2 protein. However, the effects of this compound differ from the effects of loratadine because it induced G0/G1 cell cycle arrest associated to an upregulation of p53 and p21 and a reduced kinase activities of cyclin-dependent kinase 2 (CDK2) and CDK4 (Lin *et al.*, 2007).

In addition, earlier studies demonstrated that *in vitro* and *in vivo* histamine-induced cell proliferation was blocked by H2R antagonists (Adams *et al.*, 1994; Cianchi *et al.*, 2005). These compounds suppressed the growth of murine tumour implants by inhibiting angiogenesis via reducing VEGF expression (Tomita *et al.*, 2003; Natori *et al.*, 2005). These effects also could be associated with the reduction of inflammatory cytokines and enzymes in tumour microenvironment (Takahashi *et al.*, 2001; Tomita and Okabe, 2005). In agreement with these results, clinical trials employing H2R antagonists/inverse agonists (e.g. cimetidine, ranitidine) show significant improvement in overall survival when used as adjuvant therapy in patients having curative-intent surgery (Nielsen *et al.*, 2002; Kapoor *et al.*, 2005; Deva and Jameson, 2012). On the other hand, it was recently reported that increased H2R gene expression is associated with enhanced survival in CRC patients (Gao *et al.*, 2017). Interestingly, a 30-year old work shows a marked clinical improvement and increased median survival with a daily combination treatment of subcutaneous histamine and oral H2R antagonists in a randomized study with 31 patients with advanced cancer disease and refractory to classical anticancer treatments compared with 34 non-treated patients with similar advanced cancer (Burtin *et al.*, 1988).

Considering the key role of histamine during inflammation and carcinogenesis, Tanaka *et al.* (2016a) determined the effects of H1R-H3R antagonists on inflammation-associated CRC model induced by azoxymethane (AOM, 10 mg kg<sup>-1</sup> bw, ip) and 1.5% dextran sodium

sulphate (DSS, drinking water for 7 days). Terfenadine was not able to affect tumour growth. However, the H2R antagonist (cimetidine) and the H3R antagonist and H4R agonist (clobenpropit) significantly inhibited colorectal carcinogenesis.

More recently, it was demonstrated the expression of H4R in CRC cell lines and in human colon, in which a reduced H4R expression observed in tumour samples compared to normal colonic tissue was demonstrated (Boer *et al.*, 2008). In line with these results, using genomics data from The Cancer Genome Atlas (TCGA) project and UALCAN interactive web resource (Chakravarthi *et al.*, 2017), we demonstrate that *HRH4* gene expression in patient samples is significantly reduced in primary colon adenocarcinoma compared with normal colon tissue (Figure 1A). Interestingly, H2R and H4R antagonists blocked the cell growth-promoting activity of histamine in three colon cancer cell lines without affecting the basal growth of the cells. Combination treatment with both compounds showed an additive effect on reducing the histamine-induced VEGF production and histamine-stimulated proliferation (Cianchi *et al.*, 2005). On the other hand, Fang *et al.* demonstrated that H4R inhibition resulted in reduced tumour growth and progression in CRC (Fang *et al.*, 2011).

### **Histamine receptors and oesophageal and oral cancer**

Oesophageal cancer, including both adenocarcinoma and oesophageal squamous cell carcinoma (ESCC) subtypes, is the eighth most frequent cancer worldwide and the sixth most common cause of death from cancer. Incidence and mortality are higher in less developed regions compared to more developed ones (Ferlay *et al.*, 2015; Torre *et al.*, 2015). Surgery and chemotherapy are the mainstay treatment for ESCC, which are still associated with recurrence (Kato and Nakajima, 2013).

Little is known about the participation of histamine and histamine receptors in ESCC. Previously, it was shown a significantly increased HDC-positive microvessels density in ESCC as compared with normal controls. Most of these HDC-positive cells were CD34-positive endothelial cells in microvessels with an increased proliferative capacity, suggesting that non-mast cell histamine produced in endothelial cells might play a role in regulating angiogenesis in ESCC (Li *et al.*, 2008). Recently, the expression of H4R was demonstrated in ESCC, which was closely associated with clinicopathological features, including histological grade, primary tumour size, lymph node metastasis, and patient survival. Consistently, H4R overexpression was also observed in ESCC cell lines, in which H4R activation not only blocked the cell cycle and reduced their proliferation *in vitro* but also decreased xenograft tumour growth *in vivo*. Authors proposed that the underlying mechanism involved in the inhibitory effect of H4R agonist on proliferation and invasion was the inhibition of TGF- $\beta$ 1 signalling via both a metabolic pathway (acetyl-coenzyme A synthetase 2) and a non-metabolic pathway (mitogen-activated protein kinase, MAPK) (He *et al.*, 2018). Accordingly and using TGCA data, *HRH4* gene expression level was significantly higher in tumours compared to normal oesophageal tissue (Figure 1 B).

Oral cancer is the most common form of head and neck cancer and it is associated to high mortality rate due to late diagnoses and early metastases. Among oral cancers, oral tongue squamous cell carcinoma (OTSCC) is the most frequent type and it is characterised by high metastatic potential (Ferlay *et al.*, 2015, Salem *et al.*, 2017b).

H1R was expressed in oral squamous cancer cell carcinoma (OSCC) cell lines (BICR56 and BICR3). In patient samples, H1R was rarely expressed but significantly related with advanced tumour stages. Following univariate analysis, patients with H1R expression showed a significantly poorer prognosis, suggesting that H1R activation may promote carcinogenesis in OSCC (Grimm *et al.*, 2013).

On the other hand, earlier studies show that H2R is over-expressed in OSCC developed in hamster cheek pouch. In this model and in oral cancer cell lines histamine conjugation to chlorin p6 (Cp6-histamine conjugate) improved cellular uptake and photo-toxicity of Cp6 for photodynamic treatment, producing the complete regression of large tumours and therefore improving efficacy of this treatment modality (Parihar *et al.*, 2011, 2013). In this regard, searching for more effective and selective therapies for head and neck cancer, it was demonstrated that histamine treatment ( $1 \text{ mg kg}^{-1} \text{ bw}$ , sc) improved the therapeutic effect of boron neutron capture therapy (BNCT) to treat oral cancer in the hamster cheek pouch model, reducing the BNCT-induced severe mucositis (Monti Hughes *et al.*, 2015).

Considering that gastroesophageal reflux might play a role in the aetiology of head and neck squamous cell carcinomas (HNSCC) and also contribute to complications after surgery or during radiotherapy, Papagerakis and coworkers reported in a large cohort study that routine use of anti-acid medications, including H2R antagonists, may have significant therapeutic benefit in patients with HNSCC (Papagerakis *et al.*, 2014).

Interestingly, H4R is uniformly expressed in oral epithelial cells and its immunoexpression is downregulated together with an alteration of histamine metabolism in the oral lichen planus, a premalignant lesion (Salem *et al.*, 2015, 2017a). Recently, it was reported that H4R protein staining is reduced in oral epithelial dysplasia and in all the pathological grades of OTSCC compared with the normal oral epithelium (Salem *et al.*, 2017b). Samples with the highest histopathological grade and increased mast cell counts exhibited the weakest H4R immunostaining. Consistently, expression of H4R in HSC-3 OTSCC cell line is reduced compared with the expression in normal human oral keratinocytes. Mast cells are key components of tumour microenvironment, which are implicated not only in immune modulation but also in cancer progression. In this context, authors demonstrated that mast cells release factors regulate the expression of oncogenes,

increasing the gene expression of epidermal growth factor (*EGF*) and epidermal growth factor receptor (*EGFR*) while down-regulating the expression of the anti-apoptotic genes, B-cell lymphoma 2 (*Bcl-2*) and B-cell lymphoma extra-large (*Bcl-xL*) in normal keratinocytes (Salem *et al.*, 2017b).

### **Histamine receptors and pancreatic cancer**

Pancreatic carcinoma is characterised by its silent nature of the disease and its poor prognosis. HDC expression and histamine production was reported in pancreatic cancer (Tanimoto *et al.*, 2004) and the four histamine receptor subtypes were described in pancreatic carcinoma Panc-1 cells. Proliferation studies showed that they are involved in pancreatic carcinoma cell growth, being proliferation augmented through H3R and diminished by H1R, H2R and H4R. H2R reduced proliferation through G0/G1 phase arrest, effect that was associated with a decrease in phosphoactivated extracellular signal-regulated kinase ERK1/ERK2 and involved the modulation of the Bcl-2 family proteins (Cricco *et al.*, 2004; 2006; 2008).

More recently, other authors confirmed the presence of H4R in Panc-1 and other 2 pancreatic cancer cell lines (MiaPaCa-2 and AsPC-1) but they were unable to detect the H3R. In these cell lines, clobenpropit inhibited cell proliferation and cell migration, disrupting epithelial to mesenchymal transition (ETM). Its combined effect with gemcitabine increased apoptosis of pancreatic cancer cells. In agreement with the *in vitro* results, combined therapy induced a reduction of tumour growth and enhanced apoptosis *in vivo*, in Panc-1 xenograft induced in mice (Pail *et al.*, 2014).

## Histamine receptors and liver cancer

Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide and its development is associated with inflammation, viral hepatitis, alcohol abuse and liver cirrhosis. Studies performed in HCC cells lines show that histamine produced dual effects on cell growth, decreasing proliferation in HuH-6 cell line through the H1R, which mediated the down regulation of  $\beta$ -catenin, COX-2, and survivin expression and increased apoptosis. In contrast, in HA22T/VGH cells histamine induced a weak increase in cell growth mediated through the H2R (Lampiasi *et al.*, 2007; Kennedy *et al.*, 2012). In other study, cimetidine blocked EGF-induced cellular proliferation and migration in HCC cell lines (Hep3B, HLF, SK-Hep-1, JHH-2, PLC/PRF/5 and HLE) by decreasing cAMP concentration (Fujikawa *et al.*, 2007). Recently, it was reported that an H1R antagonist, cypheptadine, reduced proliferation of HepG2 and Huh-7 HCC cells by blocking cell cycle progression through the activation of P38 MAPK, with minimal toxicity in normal hepatocytes (Feng *et al.*, 2015).

H3R is also expressed in McA-RH7777 hepatoma cells and histamine activation produced antiproliferative effects (Davenas *et al.*, 2008). To the best of our knowledge, no description of H4R in HCC cells was yet published. In the present work, using the TGCA database we show that *HRH4* gene is expressed in HCC primary tumours (n=371) and its expression is slightly increased compared to normal tissue (n=50) (Figure 1 C).

Cholangiocarcinoma (CCA) is a biliary cancer arising from damaged bile ducts and is the second most common type of cancer in the liver after HCC. When possible, is treated by surgical resection (Blechacz *et al.*, 2009).

It was demonstrated the expression of the four histamine receptor subtypes in numerous CCA cell lines, with an up regulation of *HRH3* (Onori *et al.*, 2010). On one side, long-term treatment with histamine increased proliferation and VEGF expression with no changes in



angiogenesis in human CCA developed in nude mice that were blocked by HDC inhibitor and the H1R antagonist (Francis *et al.*, 2012).

On the other side, H3R stimulation by binding to its agonist [(R)-( $\alpha$ )-(-)-methylhistamine] activated the PKC $\alpha$ -dependent pathway, leading to inhibition of CCA growth *in vitro* and *in vivo*. In this study, it was demonstrated that H3R signals via G $\alpha$ /0 and induces an increase in intracellular IP<sub>3</sub> but not cAMP signalling (Francis *et al.*, 2009). The antiproliferative effects induced by H3R were associated with a decrease in VEGFA/C and VEGF-R2/3 expression.

In line with the results in the CRC and pancreatic cancer models, clobenpropit suppressed human CCA progression, decreasing tumour invasion and growth through disruption of the epithelial-mesenchymal transition (EMT) using *in vitro* and *in vivo* model systems. The effects of clobenpropit were mediated via a Ca<sup>2+</sup>-dependent mechanism and altered morphological development and invasion. Meng and coworkers show that H4R expression levels were increased in CCA in comparison with non-malignant tissues (Meng *et al.*, 2011). Likewise, analyses of TCGA cancer genomics data show a modest significant increase in the median of *HRH4* expression levels in CCA primary tumours compared with normal tissue (Figure 1 D).

### **Histamine receptor and gastric cancer**

Gastric carcinoma (GC) is the fourth most common malignancy and remains the second cause of death worldwide. Approximately 90% of GCs are adenocarcinomas, which arise from the glands of gastric mucosa (Sitarz *et al.*, 2018).

Regulation of acid secretion by the parietal cell is the pivotal function of histamine in the stomach, demonstrated by the well-known clinical efficacy of H2R antagonists in various gastric clinical conditions (Coruzzi *et al.*, 2012).

Human enterochromaffin-like cells (ECL) and GC cells expressed high levels of HDC where it is regulated by gastrin (Höcker *et al.*, 1996). Previous studies show that histamine modulates proliferation of numerous gastric tumour cell lines through H2R (Emani *et al.*, 1983; Hahm *et al.*, 1996). In this line, cimetidine induces apoptosis in GC cells and inhibits tumour growth *in vivo* (Jiang *et al.*, 2010).

Previous clinical trials showed moderate survival benefit of gastric cancer patients after treatment with some H2R antagonists (Kubecova *et al.*, 2011; Kennedy *et al.*, 2012). In addition, it was shown the efficacy of famotidine, H2R antagonist, in reducing gastrointestinal toxicities during adjuvant chemotherapy with oral 5-fluorouracil for GC (Namikawa *et al.*, 2014). On the other side, acid suppressive drugs such as H2R antagonists are associated with an increased risk of GC (Ahn *et al.*, 2013). Recently, associations between common genetic variant of *HRH2* (-1018 GG) homozygosity and GC risk were reported (Arisawa *et al.*, 2012).

Regarding H4R, it showed a reduced expression level in GC compared to the adjacent normal tissue. In addition, both histamine and clobenpropit were able to induce G0/G1 cell cycle arrest in AGS cell line (Coruzzi *et al.*, 2012; Zhang *et al.*, 2012). Zhang *et al.* (2012) demonstrated that deletion of *HRH4* gene is present in GC cases and is closely correlated with attenuated gene expression, which was associated with tumour progression.

## Histamine receptors and skin cancer

Skin cancers are the most common neoplasias worldwide. They are classified as melanoma and non-melanoma skin malignancies. Non-melanoma skin cancer includes basal cell carcinoma and squamous cell carcinoma (Linares *et al.*, 2015). The incidence and mortality of cutaneous melanoma, the deadliest form of skin malignancies, is progressively increasing worldwide, especially among white population (Ingraffea, 2012).

Oncogene-targeted therapy and immune checkpoint blockade have shown some clinical efficacy in a subset of melanoma patients. These therapeutic approaches exhibit high toxicity, elevated costs and show a disease-free interval of only a few months. Therefore, the study of new therapeutic targets is urgently needed (Block *et al.*, 2015; Marzuka *et al.*, 2015; Bernatchez *et al.*, 2016; Prieto *et al.*, 2016).

A large body of evidence suggests that histamine regulates physiological and pathological conditions of skin (Gutzmer *et al.*, 2011; De Benedetto *et al.*, 2015). There are many studies describing the role of histamine as a modulator of proliferation in tumours, but in malignant melanoma results are somehow controversial (Massari *et al.*, 2011, 2013; Medina *et al.*, 2013).

Melanoma cells but not normal melanocytes contain large amounts of histamine, suggesting that the level of HDC is strongly associated with malignancy in the skin (Haak-Frendscho *et al.*, 2000; Pós *et al.*, 2004). Melanoma cells release a detectable amount of histamine into the medium without external stimuli, suggesting a possible autonomous histamine metabolism in melanoma cells. HDC activity was detected in WM35 and WM983 cell lines, while detectable HNMT activity was measured in WM983, M1 and HT168 lines and DAO catabolic enzyme showed very low activity in melanoma cell lines (Darvas *et al.*, 2003). In this line, the use of specific antisense oligonucleotide designed to inhibit HDC

protein synthesis, decreased the proliferation rate of human melanoma cells (WM938/B, HT168/91, WM35 and M1/15), indicating that endogenous histamine may produce autocrine regulation of proliferation (Hegyesi *et al.*, 2001). In addition, in a mouse melanoma model, over-expression of HDC enhanced tumour growth and increased metastatic potential (Pós *et al.*, 2005). In agreement with these results, murine B16F10 melanoma cells showed an up-regulated histaminergic system compared to non-cancerous melanocytes (Davis *et al.*, 2011). Recently, it was demonstrated that diphenhydramine (DPH), an H1R antagonist, induced apoptosis in melanoma cell lines while sparing normal melanocytes. It also suppressed tumour growth and prolonged survival of mice bearing B16F10 melanoma (Or *et al.*, 2016). Additionally, it was demonstrated that locally produced histamine, acting through paracrine and autocrine loops, could increase the expression of the protooncogene transcription factor Ets-1 (v-ets erythroblastosis virus E26 oncogene homolog 1) in melanoma cells via the H2R (Hegyesi *et al.*, 2005). Ets-1 regulate the expression of several genes involved in extracellular matrix (ECM) remodelling, angiogenesis, cell migration and tumour invasion, such as matrix metalloproteinase (MMP)-1, MMP-3 and integrin  $\beta$ 3 (Rothhammer *et al.*, 2004).

In addition, histamine may modulate the immune system in the local tumour microenvironment. It was suggested that melanoma-derived histamine may participate in a bi-directional interaction between the tumour cells and infiltrating tumour lymphocytes, shifting the local T-cell polarization towards predominance of Th2 cells (Mohammad, 2009).

Supporting the ability of histamine to modulate immune system, histamine dihydrochloride inhibits the formation of reactive oxygen species (ROS) from monocytes/macrophages by suppressing the activity of NADPH oxidase (NOX2) via H2R, and thus preventing the inactivation of T cells and NK cells (Blaya *et al.*, 2010; Hellstrand *et al.*, 2010). In this regard, histamine is being administered in clinical trials as an adjuvant to immunotherapy with IL-2 for the treatment of metastatic melanoma and acute myeloid

leukaemia, showing clinical benefits (Agarwala *et al.*, 2002; Perz *et al.*, 2008; Rydström *et al.*, 2017). Treatment of patients with stage IV melanoma with the combination of histamine and IL-2 increases type 1 T-cell responses, promoting the induction of melanoma-specific T cells. These effects provide a potential mechanism for the clinical efficacy of the combination therapy and encourage the study of histamine as an adjuvant to immunotherapy for other cancers (Asemissen *et al.*, 2005). In addition, histamine significantly increases cytotoxic activity of IL-2-stimulated NK cell-enriched splenocytes admixed with macrophages against B16F10 melanoma cells and YAC-1 cells. This effect is associated with production of high levels of IFN- $\gamma$  and TNF- $\alpha$  (Kozhar *et al.*, 2002). In the same line, in haematogenous metastatic models of melanoma developed by intravenous inoculation of B16F1 or B16F10 melanoma cells, lung metastasis formation was reduced in genetically NOX2-deficient mice and also with systemic treatment with histamine dihydrochloride, which enhanced the infiltration of IFN $\gamma$ -producing NK cells into lungs of wild type but not of NOX2-KO mice. The clear participation of IFN $\gamma$  in the antimetastatic effect of histamine was demonstrated using IFN $\gamma$ -deficient B6.129S7-Ifngtm1Ts /J mice, which have increased susceptibility to develop melanoma metastases and did not respond to the *in vivo* treatment with histamine (Aydin *et al.*, 2017).

Furthermore, literature suggests that those with allergy have a reduced risk of developing cancer versus the general population (Engkilde *et al.*, 2011) and that a history of asthma may be a protective factor in cutaneous melanoma (Hajdarbegovic *et al.*, 2014). On the other hand, other investigators suggest that allergies are permanent states of inflammation associated with the release of several inflammation mediators, such as cytokines that increase the risk of cancer development (Faustino-Rocha *et al.*, 2017).

The four histamine receptor subtypes were previously described in human melanoma cell lines (Hegyesi *et al.*, 2005; Pós *et al.*, 2005; Massari *et al.*, 2011). Histamine produces a dual

effect on proliferation, decreasing it through the H1R via PLC activation and its subsequent intracellular calcium mobilization, whereas it increases growth when acting through the H2R and cAMP production (Lázar-Molnar *et al.*, 2002). In contrast, histamine induced melanogenesis via H2R and growth-differentiation factor-15 in other melanoma cell lines (SK-MEL-2, B16F10 and Melan-a) (Lee *et al.*, 2012). H1R activation suppressed mRNA expression levels of the tumour suppressor insulin-like growth factor II receptor (IGF-IIR) and the antiangiogenic matrix protein fibulin-5 (FBLN5) (Poz *et al.*, 2008).

Furthermore, H1R antagonists (DPH, triprolidine, astemizol, and terfenadine) induced apoptosis in four melanoma cell lines but not in normal melanocytes or mouse embryonic fibroblasts. However, terfenadine induced DNA damage and apoptosis through the modulation of calcium homeostasis and tyrosine kinase activity, effects that were independent of the H1R signalling pathway (Blaya *et al.*, 2010). *In vivo* terfenadine treatment inhibited tumour growth in murine models (Paoluzzi *et al.*, 2009; Blaya *et al.*, 2010; Jiang *et al.*, 2010; Soule *et al.*, 2010). Furthermore, H1R antagonists (terfenadine, astemizol and triprolidine) induce apoptosis through caspase-2-dependent pathway in human melanoma cells but not in normal melanocytes and embryonic murine fibroblasts (Jangi *et al.*, 2006).

H3R activation was not able to modulate proliferation in human melanoma cells (Hegyesi *et al.*, 2005). On the other hand, H4R is functionally expressed in human melanoma cells and the use of agonists, antagonists and siRNA demonstrated that the inhibitory effect of histamine on proliferation was in part mediated through the stimulation of the H4R with the induction of G0/G1 phase of the cell cycle arrest, accelerated cell senescence and melanogenesis (Massari *et al.*, 2011; 2013; 2017). Interestingly, *in vivo* treatment with histamine and also a specific H4R agonist, JNJ28610244, not only demonstrated a reduction in human 1205Lu tumour growth developed in nude mice, but also reduced the metastatic spread and angiogenesis (Massari *et al.*, 2017).

It is important to highlight that the presence of H4R was demonstrated in benign and malignant lesions of melanocytic lineage emphasizing the potential clinical use of histamine receptor ligands for the treatment of melanoma. H4R expression level in benign lesions was significantly higher than in malignant tissues. In tumours, H4R receptor expression was inversely correlated with PCNA expression and mitotic index, both proliferation and prognostic markers (Massari *et al.*, 2017). Further studies are needed to corroborate the potential of H4R as a target for the treatment of this disease.

Despite melanoma has conventionally been considered as a radioresistant cancer (Khan *et al.*, 2011), combined radiotherapy and targeted therapies or immunotherapy has led to resurgence of radiotherapy (Fort *et al.*, 2016). In this regard, recent results indicate that histamine enhances the response against ionising radiation of 1205Lu melanoma cells *in vitro* and *in vivo*. Histamine produced a G2/M cell cycle arrest, increased apoptosis, DNA damage and lipid peroxidation in irradiated 1205Lu melanoma cells (Massari *et al.*, 2017).

### **Histamine receptors and breast cancer**

Breast cancer is the most frequently diagnosed neoplasia in women worldwide. This is a heterogeneous disease in terms of presentation, molecular profile and clinical response to therapy, and represents the second and first leading cause of cancer death among females in more and less developed countries, respectively (Ferlay *et al.*, 2015; Torre *et al.*, 2015).

In particular, triple-negative breast cancer (TNBC) characterized by the lack of expression of the oestrogen receptor (ER), progesterone receptor and human epidermal growth factor 2 receptor (HER2) proteins, accounts for approximately 15% of breast cancers. This breast cancer subtype exhibits poor prognosis and represents an important area of research for novel specific targeted therapy (Sotiriou *et al.*, 2003; Cleator *et al.*, 2007; Brouckaert *et al.*, 2012).

Histamine plays a critical role in the (patho)physiological conditions of the mammary gland (Davio *et al.*, 1994; Pós *et al.*, 2004; Medina and Rivera, 2010; Medina *et al.*, 2013). Higher histamine concentration was observed in human breast tumours, human cell lines and N-nitroso-N-methylurea (NMU)-induced rat mammary adenocarcinomas compared with their normal counterparts, which led to increased histamine levels in plasma derived from ductal breast cancer patients compared to healthy group, suggesting a direct correlation of endogenous histamine levels with malignancy of breast cancer (Rivera *et al.*, 2000; Sieja *et al.*, 2005; Medina *et al.*, 2006; von Mach-Szczypiński *et al.*, 2009; Medina *et al.*, 2013). Recent findings in Chinese Han population showed that polymorphisms of *HDC* gene, but not of histamine N-methyltransferase (*HNMT*) gene, were associated with breast cancer further highlighting the importance of HDC in this disease (He *et al.*, 2014).

The regulatory role of H1R and H2R on breast cancer proliferation has been extensively investigated in different animal models (Medina *et al.*, 2013; Martinel Lamas *et al.*, 2017). In NMU-induced experimental mammary carcinomas, astemizole (H1R antagonist) treatment increased the number of tumours per rat while treatment with H2R antagonists (ranitidine or cimetidine) decreased tumoural incidence (Rivera *et al.*, 1993; 2000; Davio *et al.*, 1995). The histamine-induced proliferation was mediated through H2R via the PLC-dependent pathway, while its inhibitory effect was associated to cAMP-dependent mechanism through the activation of the H1R (Rivera *et al.*, 1993; Davio *et al.*, 1995).

The presence of H1R and H2R in human normal and malignant breast cancer tissues and cell lines was further described (Davio *et al.*, 1993; 2002; Lemos *et al.*, 1995; Medina *et al.*, 2013). H2R produced an increase in cAMP levels while H1R was coupled to PLC activation in benign lesions. On the other hand, H1R was invariably linked to PLC pathway but H2R stimulated both signalling pathways in carcinomas (Davio *et al.*, 1993).



It was recently reported that H1R is up-regulated in basal and HER2-enriched human breast tumours, in which its expression correlated with a worse prognosis. Terfenadine inhibited proliferation, activated ERK signalling, initiating the mitochondrial apoptotic pathway *in vitro*. Moreover, *in vivo* studies demonstrated that terfenadine administration reduced the tumour growth of basal and trastuzumab-resistant breast cancer cells (Fernández-Nogueira *et al.*, 2018). In addition, another H1R antagonist, astemizole, combined with histamine induced autophagy and apoptosis targeting p53-dependent crosstalk in human MCF-7 breast cancer cells (Jakhar *et al.*, 2016).

Oral ranitidine treatment decreased the monocytic myeloid derived suppressor cells (MDSC) population in the spleen and bone marrow in the context of orthotopic murine breast tumour models, which affects breast tumour development and progression. It inhibited lung metastasis in the 4T1 model and decreased primary tumour growth in E0771 model (Vila-Leahey *et al.*, 2016a). In addition, oral ranitidine treatment was associated with the development of enhanced antitumor antibody responses in E0771-GFP orthotopic tumour-bearing mice, modulating B cell populations. In agreement with these results, ranitidine was not able to decrease primary tumour growth in B cell-deficient animals, highlighting the importance of this commonly used H2R antagonist as modulator of antitumour immunity in breast cancer (Rogers *et al.*, 2018).

However, ranitidine administration failed to reduce tumour growth in the B16F10 melanoma, LLC1 lung cancer and EL4 lymphoma models (Vila-Leahey *et al.*, 2016b).

Despite promising preclinical data, the clinical trials carried out with H2R antagonists lead to inconclusive results for breast cancer patients (Bowrey *et al.*, 2000; Parshad *et al.*, 2005). In addition, it was recently showed that the use of H2R blockers overall, cimetidine and famotidine was not associated with an increased risk of breast cancer, while current users of

ranitidine had a 2.2-fold increased risk of developing ductal carcinoma (Mathes *et al.*, 2008). No significant associations of rs2067474 polymorphism of human *HRH2* with breast cancer risk or with related clinicopathological parameters were observed in Chinese Han population (Cai *et al.*, 2015). According to the evidence, the treatment with H2R antagonists seems not to be useful from a therapeutically point of view.

It is important to point out that the H3R is also expressed in human cell lines and biopsies of benign lesions and breast carcinomas, being the level of its expression significantly higher in carcinomas, where its expression is highly correlated with proliferation and histamine production (Medina *et al.*, 2008; He *et al.*, 2014). *In vitro* studies showed that histamine modulated the proliferation of the TNBC cell line MDA-MB-231, in a dose-dependent manner, reducing cell growth mainly through the H4R and slightly increasing it via H3R, acting on the cAMP pathway (Medina *et al.*, 2006; 2008; 2011). In line with these results, it was recently shown that the H3R antagonist OUP-186 potently suppressed proliferation and induces caspase-dependent apoptosis in breast cancer cells (Tanaka *et al.*, 2016b).

The antiproliferative effect of histamine in MDA-MB-231 and MCF-7 cells was associated with the induction of cell cycle arrest, cell differentiation and apoptotic cells with modulation of ROS levels (Medina *et al.*, 2006; 2008). In line with *in vitro* data, *in vivo* administration of the JNJ10181457 (H3R antagonist), produced a decrease in the volume of MDA-MB-231 xenograft tumours established in immune deficient nude mice (Martinel Lamas *et al.*, 2013).

The discovery of the human H4R more than a decade ago has helped refine our understanding of histamine functions in cancer development and progression (Medina and Rivera, 2010). It was shown that H4R protein is expressed in malignant lesions derived from the human mammary gland and also is expressed in MDA-MB-231 and MCF-7 breast cancer

cell lines (Medina *et al.*, 2006; 2008). Accordingly, using TCGA data we show, in a large number of human samples, that *HRH4* gene expression is significantly reduced in primary tumours compared with normal tissue (Figure 2 A). Furthermore, the presence of polymorphisms of the *HRH4* gene in variants of rs623590, rs11662595 and rs1421125 genotypes of *HRH4* gene were associated with the risk and malignant degree of breast cancer in Chinese Han population (He *et al.*, 2013), supporting the hypothesis of the importance of H4R in breast cancer development and progression. By means of the use of pharmacological and genetic tools, it was demonstrated that the main receptor subtype involved in the histamine-induced inhibitory response on proliferation was the H4R (Medina *et al.*, 2008; 2011; Martinel Lamas *et al.*, 2013). H4R agonists induced cell cycle arrest, augmenting the number of apoptotic and senescent cells (Medina *et al.*, 2011; Martinel Lamas *et al.*, 2013). In line with *in vitro* results, *in vivo* histamine and an H4R agonist (JNJ28610244) administration diminished the proliferation of MDA-MB-231 tumours developed in nude mice. Histamine was able to increase median survival and tumoural apoptosis (Martinel Lamas *et al.*, 2013).

It is important to highlight that histamine not only exhibits an anti-tumoural action but it is also able to potentiate the effects of conventional therapies such as ionizing radiation and doxorubicin chemotherapy in breast cancer *in vitro* and *in vivo* models.

Histamine produces a radiosensitising action involving enhanced radiation-induced oxidative DNA damage, DNA double-strand breaks, apoptosis and senescence, effects that were related to an increased production of ROS through the inhibition of catalase, glutathione peroxidase and superoxide dismutase activities in MDA-MB-231 cells (Medina *et al.*, 2006; Martinel Lamas *et al.*, 2015a). In these cells, histamine pre-treatment prevented the radiation-induced mesenchymal changes (e.g. decrease in the epithelial marker E-cadherin, increase in the mesenchymal marker vimentin and Slug and MMP-2 activity) and

reduced the migratory behaviour of irradiated cells decreasing phospho-Src levels (Galarza *et al.*, 2016). Furthermore, histamine was able to enhance the effect of gamma radiation *in vivo*, augmenting the exponential tumour doubling time of TNBC developed in nude mice (Medina *et al.*, 2006; Martinel Lamas *et al.*, 2015a). Importantly, *in vivo* studies show that histamine was also safely used in different experimental models as a radioprotective agent of normal radiosensitive tissues, including small intestine, salivary glands and bone marrow (Medina *et al.*, 2007, 2010, 2011; Carabajal *et al.*, 2012). In this regard, it was recently reported that histamine exhibits chemoprotective effects against doxorubicin-induced cytotoxic and oxidative damage in heart and liver, without compromising the anti-tumour activity of doxorubicin (Martinel Lamas *et al.*, 2015b, 2015c).

In the context of the complexity of cancer disease, future anti-cancer treatments should consider the tumour and the interactions with its microenvironment. In this regard, conditioned media derived from fibroblasts induced EMT phenotypic changes in MCF-7 and MDA-MB-231 breast cancer cells, effects that were reversed with histamine treatment (Porretti *et al.*, 2014).

It is well known that histamine is an important mediator of immunologic reactions (Jutel *et al.*, 2009; Stark 2013). Previous data demonstrated that histamine can modulate antigen-specific T helper (Th) cells by changing the cytokine production from a Th1 to a Th2 pattern (Shankaran *et al.*, 2001, Holger 2013). On the one hand, in a HDC KO model, endogenous histamine contributed to the growth of murine LM2 breast tumour by suppressing the antitumor immunity (Hegyesi *et al.*, 2007). On the other hand, histamine treatment stimulates the maturation of dendritic cells from monocytes, reducing the growth of murine lymphoma developed with EL-4 cells (Martner *et al.*, 2015). A recent work shows for the first time the role of H4R in antitumor immunity in a model of TNBC developed orthotopically with 4T1 cells in H4R KO compared with wild type mice. Mice lacking H4R show reduced tumour

growth, decreased number of lung metastases and percentage of CD4<sup>+</sup> tumour-infiltrating T cells while they show increased infiltration of natural killer (NK) cells. In addition, tumour draining lymph nodes show decreased CD4<sup>+</sup> T cells and T regulatory cells (Tregs) (CD4<sup>+</sup>CD25<sup>+</sup>FoxP3<sup>+</sup>) (Sterle *et al.*, 2018). Therefore, different histamine metabolism, distinct tumour microenvironment and the availability of histamine receptors, may determine the histamine receptor ligand-induced outcome.

### **Histamine receptors and lung cancer**

Lung cancer was the most frequently diagnosed cancer and the leading cause of cancer death among males in 2012. Among females, lung cancer was the leading and the second leading cause of cancer death in more developed countries and in less developed countries, respectively (Ferlay *et al.*, 2015; Torre *et al.*, 2015). Non-small cell lung cancer (NSCLC) is the most common form of lung cancer and is characterized by a chronic inflammatory process, which is associated with high mast cell infiltration and reduced survival rate (Stoyanov *et al.*, 2012). Previous data suggest that histamine is involved in the pathogenesis of lung cancer, considering that a significant decrease in histamine plasma levels was observed in patients with lung cancer compared to the healthy subjects. Interestingly, smoking significantly reduced the histamine plasma levels just in cancer patients (Della Rovere *et al.*, 2006).

In experimental models, it was found a dual effect of mast cell infiltrate and histamine in lung tumours. On the one hand, mast cells and histamine increased human alveolar basal adenocarcinoma (A549) and mouse Lewis lung carcinoma (LLC) cell proliferation *in vitro*, via H1R, H2R and H4R and ERK phosphorylation. On the other hand, mast cells resulted in

antitumoural effects in the *in vivo* mouse LLC model (Stoyanov *et al.*, 2012). In addition, combination of astemizole-gefitinib reduced proliferation while increased apoptosis in A549 cells (Chávez-López *et al.*, 2017). In line with these results, antihistamines induced lysosomal cell death of NSCLC cells and sub-micromolar concentrations of loratadine and astemizole sensitised NSCLC cells to chemotherapy and reversed multidrug resistance. A cohort study on the effect of widely used antihistamine drugs on mortality of patients diagnosed with non-localised cancer in Denmark show that loratadine use was associated with significantly reduced all-cause mortality among patients with non-localised NSCLC (Ellegaard *et al.*, 2016).

As it was reported in other tumour subtypes, cimetidine inhibited growth of murine 3LL lung tumours. Although cimetidine showed no antitumoural effects *in vitro*, it reduced CD11b<sup>+</sup>Gr-1<sup>+</sup>MDSC accumulation in spleen, blood and tumour tissue of tumour-bearing mice (Zheng *et al.*, 2013).

Recently, it was suggested that H4R may have an important role in preventing EMT progress in NSCLC (Cai *et al.*, 2014). Treatment with 4-methylhistamine increased the expression of the epithelial marker E-cadherin and decreased the expression of the mesenchymal marker vimentin, in both NSCLC cell lines and xenograft tumours. This effect was reversed with a pre-treatment with the H4R antagonist JNJ7777120 or by *HRH4* gene silencing (Cai *et al.*, 2014). Moreover, recent investigations suggested that genetic variations of *HRH4* gene affected H4R function, which could lead to predisposition to H4R-related diseases. Cai *et al.* (2017) demonstrated that the loss-of-function polymorphism rs11662595 significantly decreased the ability of H4R to activate Gi protein, which resulted in cell proliferation, facilitation of EMT progress, and invasion behaviour *in vitro*. In a prospective cohort study among 624 NSCLC patients, the investigators proved that rs11662595 was responsible for the prognosis, degree of malignancy and metastasis of NSCLC (Cai *et al.*,

2017). Accordingly, and further supporting the relevance of the H4R in lung cancer, genomic data from TCGA show that *HRH4* gene expression is significantly reduced in tumours in relation to normal tissue samples (Figure 2 B).

### **Histamine receptors and haematological malignancies**

A haematological malignancy is a collective term for a cancer of the haematopoietic and lymphoid tissues, with clinical presentation as leukaemia, lymphoma, or myeloma. Approximately every 10 minutes, someone in the US dies from a blood cancer while an estimated of more than a million people in the US are living with, or are in remission from, these neoplastic diseases (Cancer Facts & Figures, 2012).

It is well established the participation of histamine in the regulation of haematopoiesis and also in haematological malignancies (Byron, 1977; Medina *et al.*, 2013). Interestingly, it was demonstrated that HDC KO exhibited an increased rate of colon and skin carcinogenesis compared to wild type mice, associated to a reduced histamine-induced differentiation of immature myeloid cells (Yang *et al.*, 2011).

The histamine levels were higher in lymph nodes of patients with malignant lymphomas, Hodgkin's disease (HD) or non-Hodgkin lymphomas (NHL) when compared with control individuals (Belcheva and Mishkova, 1995). In addition, acute lymphocytic leukaemia (ALL) cells exhibited histamine content and H1R antihistamines inhibited their clonogenic growth (Malaviya *et al.*, 1996). It was suggested that the proapoptotic effect of H1R antagonist (e.g.diphenhydramine) could be associated with the inhibition of voltage-gated proton channels (Hv1) that induced intracellular acidification and reduction of leukaemic Jurkat T

cells viability (Asuaje *et al.*, 2018). Furthermore, the promonocytic U-937 cell line, derived from a histiocytic lymphoma, show a switch of histamine receptor expression from H2R to H1R during differentiation of monocytes into macrophages (Wang *et al.*, 2000). Histamine or H2R agonists, which increased cAMP levels, failed to promote differentiation of U-937 cells due to rapid homologous and GRK2 dependent desensitization of H2R (Fernández *et al.*, 2002). In addition, in U937 and other acute myeloid leukaemia (AML) cell lines, amthamine (H2R agonist), augmented intracellular cAMP levels with a concomitant increase in the efflux regulated by multidrug resistance-associated proteins (MRPs), particularly MRP4 (Copsel *et al.*, 2011). Martnet *et al.*, (2015) further highlights the involvement of histamine in lymphoma progression. Histamine treatment induced intratumoural accumulation of matured dendritic cells, reducing the growth of murine lymphoma developed with EL-4 cells (Martner *et al.*, 2015).

Most patients with AML achieve complete remission after induction chemotherapy. However, a large number of patients will experience relapses with poor prospects of long-term survival. IL-2 and interferon-alpha (IFN $\alpha$ ) are effective activators of lymphocytes with anti-neoplastic properties, such as T-cells or NK cells. *In vitro* data suggest that those immunotherapeutic cytokines only weakly activate T cells or NK cells in a reconstituted environment of oxidative stress. As previously indicated, numerous clinical trials were performed with IL-2 immunotherapy for solid neoplastic diseases and haematopoietic cancers supplemented with histamine dihydrochloride. The reason of the combination was to counteract the immunosuppressive signals from monocytes/macrophages, inhibiting the formation of ROS that suppresses the activation of T cells and NK cells, through reducing the activity of NADPH oxidase via H2R. This combination improved leukaemia-free survival but lacked power to detect an overall survival (OS) difference in AML patients (Hellstrand *et al.*, 2000; Brune *et al.*, 2006; Martner *et al.*, 2010; Berry *et al.*, 2011; Buyse *et al.*, 2011; Yang &



Perry, 2011). Aurelius *et al.* (2012) demonstrated that leukaemia-free survival was strongly improved in M4/M5 (myelomonocytic/monocytic) but not in M2 (myeloblastic) leukaemia. M4/M5 cells, but not M2 cells, expressed H2R and produced ROS that triggered apoptosis in adjacent NK cells. Both effects were inhibited by histamine dihydrochloride, suggesting that H2R expression on different types of human AML cells could influence the effectiveness of histamine-based immunotherapy (Aurelius *et al.*, 2012). In line with these results, it was recently described a direct therapeutic benefit of histamine treatment on NOX2+ human monocytic leukaemia cells. These cells increased expression of maturation markers along with reduced cell proliferation after exposure to histamine *in vitro*, effects that were absent in corresponding leukaemia cells genetically depleted of NOX2 (NOX2-/-). Histamine additionally modulated gene expression involved in differentiation and cell cycle progression, inducing differentiation of AML cells and also of primary monocytic, but not non-monocytic AML cells *in vitro*. Importantly, histamine treatment reduced the *in vivo* expansion of NOX2+/, but not of NOX2-/- human monocytic AML cells (Kiffin *et al.*, 2018). Histamine/IL-2 immunotherapy implied the induction of immunosuppressive Tregs cells that may be targeted for improving the therapeutic efficiency of the combined therapy (Sander *et al.*, 2017). It is worth noting that histamine dihydrochloride administration has been approved in Europe for the treatment of adults with AML, used in combination with IL-2. A recent study in Chinese healthy volunteers shed light in the safety profile and pharmacokinetic properties of a single dose of histamine (0.5 mg or 1 mg), showing that both single doses were well tolerated (Li *et al.*, 2015). Approval of this therapeutic combination was based on phase III trial results that showed significantly reduced relapse risk in patients who received the combined therapy. In an international phase IV trial, 84 patients with AML in first complete remission received immunotherapy with histamine dihydrochloride and low-dose

IL-2. Myeloid cell counts and expression of activation markers correlated with clinical outcome in terms of relapse risk and survival (Rydström *et al.*, 2017).

Further studies are needed to better understand role of histamine in blood cancers aiming to improve cancer immunotherapy efficacy.

### **Mast cells, basophils and histamine in cancer**

Information on the immunomodulatory role of histamine on different immune cell subsets is vast and grows exponentially and therefore this issue will be the focus of another topic review. Considering the important role of histamine producing immune cells in the tumour microenvironment affecting the development, progression of cancer and even though the response to therapy, in this section we aim to briefly summarise the controversial role of the major sources of histamine, mast cells and basophils. Mast cells and basophils play a key role in type I allergy, as well as in innate and adaptive immune responses (Ennis *et al.*, 2013; Stark 2013; Varricchi *et al.*, 2018). Both immune cell types have morphological similarities and functions however, basophils mature and are released into the blood from bone marrow while mast cells originate from myeloid precursors that usually mature in tissues, including skin, lung and gastrointestinal tract. Allergen-induced activation of mast cells and basophils results in the release of numerous inflammatory mediators, including histamine (reviewed in Ennis *et al.*, 2013; Varracchi *et al.*, 2018). Histamine modulates, in an autocrine way, the function of mast cells and basophils, including their ability to further degranulate. Both granulocytic immune cells expressed H1R, H2R and H4R. H4R activation produces calcium mobilization, actin polymerization, and cell shape change, inducing chemotaxis and

modulating the release of cytokines and chemokines (Ennis *et al.*, 2013; Mommert *et al.*, 2016; Varricchi *et al.*, 2018). Mast cell infiltration has been shown in several types of human tumours and in animal cancer models, associated either to good or poor prognosis depending on tumour type, tissue localization and the ability of mast cells to interact with extracellular matrix, tumour cells and immune cells (reviewed in Faustino-Rocha *et al.* 2017; Kennedy *et al.*, 2012, Rigoni *et al.*, 2015). Histamine and other secreted mediators such as heparin, serine proteases and prostaglandins among others, with modulatory functions, could promote invasion and angiogenesis by increasing capillary permeability and inducing remodelling of the adjacent stroma (Rigoni *et al.*, 2015). Data are contradictory, there are numerous reports supporting the protumoural (promotion of tumour growth, angiogenesis, immunosuppression and tumour invasion) and also the antitumoral (inhibition of the tumour growth and metastasis, induction of apoptosis, stimulation of inflammation) roles of mast cells and basophils, depending on the different clinical or experimental context and different type of tumour (Ribatti and Crivellato, 2012; Faustino-Rocha *et al.*, 2017). Some authors correlated the increase in mast cells number with poor prognosis in human melanoma, OSCC and prostate cancer. In addition, a positive correlation between mast cells number and microvessel density was also reported in ESCC, GC, CRC, HCC, OSCC and melanoma (Elpek *et al.*, 2001; Ch'ng *et al.*, 2006; Faustino-Rocha *et al.*, 2017). Particularly, in breast cancer, their function is still under evaluation. On the one hand, *in vitro* and *in vivo* studies show a protumour activity through promotion of lymphatic and blood vessel formation, tumour growth, and metastasis. On the other hand, clinical data demonstrated that the higher the level of mast cells the greater survival and favourable prognosis (reviewed in Aponte-Lopez *et al.*, 2018).

Less information describing basophils role in cancer is available. Marked basophilia represents a relevant independent prognostic variable in chronic myeloid leukaemia (CML). Basophils are unique sources of inflammatory, angiogenic and fibrogenic mediators. In addition, basophils may produce autocrine growth factors for myeloid cells. The better understanding of the role of basophils in CML could help to support the development of more effective treatment concepts (Valent *et al.*, 2018).

Further research is necessary to fully understand the role of mast cells and basophils in cancer, which may help to define whether a new target on these cells could be used for the adjuvant treatment of tumours by inhibiting angiogenesis, tissue remodelling and tumour growth.

### **Polyamines and histamine in cancer. Brief commentary**

The polyamines are organic polycationic alkylamines derived from aromatic or cationic amino acid, which together with histamine are widely distributed in mammalian cells and play essential roles in many relevant physiological processes (Pegg *et al.*, 2011; Medina *et al.*, 2003). Polyamine biosynthesis begins with the hydrolysis of arginine by arginase to produce putrescine by the decarboxylation of the amino acid ornithine by ornithine decarboxylase (ODC). Subsequent addition of an aminopropyl group to putrescine leads to the synthesis of spermidine and further addition of another aminopropyl group forms spermine (Russell *et al.*, 2001; Ennis *et al.*, 2013). Polyamines contribute to mast cell granule conformation together with other biogenic amines such as histamine and serotonin.

Therefore, mast cell is an excellent model to investigate the physio/pathological interplay among biogenic amines. In these immune cells and other mammalian cells, opposite activation patterns were shown among biosynthetic pathway of both histamine and

polyamines (Garcia-Faroldi *et al.*, 2009; Ennis *et al.*, 2013). Newly synthesised histamine produced an inhibitory effect on both growth-related polyamine biosynthesis and cell cycle progression of non-fully differentiated mammalian cells (HEK-293 cells) (Abrighach *et al.*, 2010; Caro-Astorga *et al.*, 2014).

Polyamines are involved in several cellular functions from DNA stabilization, and regulation of gene expression to ion channel function and, principally, cell proliferation in rapidly dividing cells (e.g. immune system and digestive tract). For that reason, polyamines are also involved in the carcinogenic process (Ramani *et al.*, 2014; reviewed in Fernández-Reina *et al.*, 2018). Multiple abnormalities in the control of polyamine metabolism and uptake might be responsible for increased levels of polyamines in cancer cells as compared to that of normal cells. In cancer, polyamine metabolism is frequently dysregulated, indicating that elevated polyamine levels are necessary for tumour development, progression and maintenance of the neoplastic phenotype, mainly through an up-regulation of polyamine biosynthetic enzymes (Thomas *et al.*, 2003; Murray-Stewart *et al.*, 2013; Cervelli *et al.*, 2014; Ramani *et al.*, 2014). Breast cancer patients show higher expression of ODC in breast cancer tissue compared with that of the normal tissue, being the expression of ODC positively correlated with TNM stages (Deng *et al.*, 2008). Another example of the participation of polyamines in cancer is their role in CRC. Polyamines are involved in almost all the steps of colorectal tumorigenesis and consequently, their biosynthesis and catabolism can be considered as promising targets for cancer chemoprevention (reviewed Linsalata *et al.*, 2014; Fernández-Reina *et al.*, 2018).

Interestingly, many findings reveal a link between the polyamines/histamine metabolic interplay and the development of cancer pathology (Medina *et al.*, 1999; Garcia-Faroldi *et al.*, 2009; Fernández-Reina *et al.*, 2018). For instance, polyamine and histamine-related metabolites are differently detected in breast cancer cells compared with their normal

counterparts. In this light, to further improve therapeutic strategies for cancer treatment, the role of the polyamine/histamine metabolic interaction in each cancer type should be precisely investigated.

## CONCLUSIONS AND PERSPECTIVES

In the present review, we have presented major findings of the most recent research on histamine and histamine receptors in cancer. From cell lines, to animal models and human clinical trials, there is now overwhelming evidence supporting the significance of histamine receptors in cancer formation and spread, producing protumoural or antitumoural effects (Figure 3).

Different histamine metabolism, distinct tumour microenvironment and the histamine receptor that is involved together with its associated signalling pathway, may determine the outcome in diverse types of cancer. Present findings demonstrate that histamine through H4R plays important roles at a variety of stages during tumour development and in multiple cell types including cancer cells and cells of tumour microenvironment (Figure 3). Future efforts are needed to better understand the molecular pathways triggered by H4R in tumour cells in interaction with the tumour microenvironment, in order to refine the knowledge of H4R that could open new perspectives in histamine pharmacology research that aims to develop a new generation of ligands targeting the H4R for advances in the treatment of cancer.

In most cancer types including CRC, OTSCC, GC, melanoma, breast cancer, LSCC, and also bladder urothelial carcinoma (Figure 2 C) and uterine corpus endometrial carcinoma (Figure 2 D), H4R gene and/or protein expression is significantly reduced in tumours in comparison with normal tissue. In addition, H4R expression was associated to

clinicopathological characteristics and possibly to the degree of cancer cell differentiation and tumour progression, suggesting that H4R might represent novel potential prognostic biomarker.

It is important to highlight that histamine is able to enhance conventional antitumour therapies in different cancer types, supporting the rationale for the use of combination therapy with histamine in clinical settings. In this connection, both histamine and numerous histamine receptor ligands are approved for use in humans, reducing the gap between experimental work and potential clinical application.

After one century of Sir Henry Dale discovery, histamine continues offering new functions and contributing to the identification of potential targets for cancer treatment.

## **NOMENCLATURE OF TARGETS AND LIGANDS**

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017).

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## **CONFLICT OF INTEREST**

The authors have no conflict of interest to declare.

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**Table 1: Main characteristics of histamine receptors**

	<u><a href="#">H<sub>1</sub> receptor</a></u>	<u><a href="#">H<sub>2</sub> receptor</a></u>	<u><a href="#">H<sub>3</sub> receptor</a></u>	<u><a href="#">H<sub>4</sub> receptor</a></u>
Location	Ubiquitous: smooth muscle, endothelial cells, nerve cells, chondrocytes, hepatocytes, T and B lymphocytes, monocytes, eosinophils, neutrophils, cancer cells	Ubiquitous: smooth muscle, endothelial cells, nerve cells, chondrocytes, hepatocytes, T and B lymphocytes, monocytes, eosinophils, neutrophils, cancer cells	Mainly in CNS and histaminergic neurons, some cancer cells	Mainly in hematopoietic cells, leukocytes, lung, intestinal epithelium, spleen, stomach, CNS, nerves of the nasal mucosa, enteric neurons, cancer cells
Number of Amino Acids	487	359	445	390
G protein coupling	G $\alpha_{q/11}$	G $\alpha_s$	G $\alpha_{i/o}$	G $\alpha_{i/o}$
Main signalling pathways	<p>↑ PLC → ↑ IP<sub>3</sub> + ↑ DAG → Increase in Ca<sup>2+</sup> → ↑ PKC</p> <p>cAMP accumulation via G<math>\beta\gamma</math> subunits of G<math>_q</math></p>	<p>↑ AC → ↑ cAMP → ↑ PKA</p> <p>↑ PLC → ↑ IP<sub>3</sub> + ↑ DAG → Increase in Ca<sup>2+</sup> → ↑ PKC</p>	↓ cAMP, Increase in Ca <sup>2+</sup> , ↑ MAPK	↓ cAMP, Increase in Ca <sup>2+</sup> , ↑ MAPK
Agonists	2-[(3-trifluoromethyl)phenyl] histamine, <u><a href="#">Histaprodifen</a></u> , <u><a href="#">Methylhistaprodifen</a></u>	<u><a href="#">Amthamine</a></u> , <u><a href="#">Impromidine</a></u>	<u><a href="#">RMHA</a></u> , <u><a href="#">Imetit</a></u> , <u><a href="#">Immepip</a></u>	<u><a href="#">VUF 8430</a></u> , <u><a href="#">Clobenpropit</a></u> , JNJ28610244, <u><a href="#">4-methylhistamine</a></u> , <u><a href="#">ST-1006</a></u> , Imetit
Antagonists / inverse agonists	<u><a href="#">Pyrilamine</a></u> , <u><a href="#">Terfenadine</a></u> , <u><a href="#">Cyproheptadine</a></u> , <u><a href="#">Loratadine</a></u> , <u><a href="#">DPH</a></u> , <u><a href="#">Triprolidine</a></u> , <u><a href="#">Astemizol</a></u> , <u><a href="#">Chlorpheniramine</a></u>	<u><a href="#">Cimetidine</a></u> , <u><a href="#">Ranitidine</a></u> , <u><a href="#">Tiotidine</a></u> , <u><a href="#">Famotidine</a></u>	Clobenpropit, <u><a href="#">JNJ5207852</a></u> , JNJ10181457, OUP-186, <u><a href="#">Pitolisant</a></u> , <u><a href="#">Thioperamide</a></u>	<u><a href="#">JNJ7777120</a></u> , <u><a href="#">Thioperamide</a></u> , <u><a href="#">JNJ10191584</a></u> , <u><a href="#">VUF 6002</a></u> , A-987306, A-940894, OUP-16
HGNC	<i>HRH1</i>	<i>HRH2</i>	<i>HRH3</i>	<i>HRH4</i>
Gene structure	Intronless	Intronless	Three introns	Two introns
Chromosomal location	3p25.3	5q35.2	20q13.33	18q11.2

**AC**, adenylate cyclase; **cAMP**, 3',5'-cyclic adenosine monophosphate; **DAG**, diacylglycerol; **DPH**: Diphenhydramine; **IP3**, 1,4,5- inositol triphosphate; **MAPK**, mitogen-activated protein kinase; **PKA**, protein kinase A; **PKC**, protein kinase C; **PLC**, phospholipase C; **RMHA**, R- $\alpha$ -methylhistamine; **SNC**, central nervous system;  $\uparrow$ , activation or formation;  $\downarrow$ , inhibition or reduction;  $\rightarrow$  induction or production.

Extracted and adapted from Shahid *et al.*, 2009 and Panula *et al.*, 2015.

Drugs and molecular targets conform to BJP's Concise Guide to Pharmacology (Alexander *et al.*, 2015).

Accepted Article

**Table 2: Recent clinical trials using histamine receptor ligands**

Type of ligand	Compound	Study Characteristics/ Pathology	Results	Drug Indication	Reference
<b>H1R antagonist</b>	<a href="#">Fexofenadine</a>	Atopic dermatitis (AD)	Severity of pruritus decreased compared with placebo	60 mg twice daily orally administered for 7 days	Ohsawa <i>et al.</i> , 2014
	<a href="#">Doxepin</a> , <a href="#">Diphenhydramine</a> <a href="#">Loratadine</a>	AD	Beneficial effects	Topical	Ohsawa <i>et al.</i> , 2014
<b>H2R antagonist</b>	Lafutidine	Twenty patients with taxane-induced peripheral neuropathy during the treatment of gynaecological malignancy (pilot study)	High efficacy for the treatment of taxane-induced peripheral neuropathy	20 mg daily orally administered for 2-4 weeks	Nagano <i>et al.</i> , 2012
	Lafutidine	Patients with stage II (T1 cases excluded) or stage III gastric adenocarcinoma	Prevents gastrointestinal toxicities during adjuvant chemotherapy for gastric cancer and improves compliance with taking oral fluorouracil anticancer drugs.	10 mg daily orally administered for 2,4 or 6 weeks	Namikawa <i>et al.</i> , 2014
	<a href="#">Famotidine</a>	116 patients with bleeding gastroduodenal ulcers	Similar effects to an adjuvant therapy for preventing rebleeding from endoscopically treated upper gastrointestinal bleeding	20 mg daily injected during the early phase of bleeding	Sakurada <i>et al.</i> , 2012
<b>H3R antagonist</b>	<a href="#">Pitolisant</a> (BF2.649)	Randomized, double-blind, parallel-controlled trial in patients with narcolepsy	At doses up to 40 mg was efficacious on EDS compared with placebo and well tolerated compared with modafinil.	10, 20 or 40 mg daily of pitolisant; 100, 200 or 400 mg daily of modafinil for 8 weeks	Dauvelliens <i>et al.</i> , 2013
	Pitolisant (BF2.649)	14 adult patients with epilepsy in early phase II	Photosensitive response reduction	60 mg single oral dose	Kasteleijn-Nolst <i>et al.</i> , 2013
	Betahistine hydrochloride (betaserc)	980 patients in the treatment of disturbance of balance system. The study was based on analysis of doctors and patients questionnaires	Improvement of vertiginous symptoms	48 mg daily orally administered for 14-28 days	Kantor <i>et al.</i> , 2006; Amini <i>et al.</i> , 2015

<b>H4R antagonist</b>		results/or treatment of peripheral vertigo			
	Pitolisant (BF2.649)	Randomized, double-blind, placebo-controlled trial in patients with narcolepsy and with cataplexy	Efficacious reduction of cataplexy	5 to 40 mg daily orally administered for 7 weeks	Szakacs <i>et al.</i> , 2017
	<a href="#">JNJ-39758979</a>	Phase IIa study in patients with moderate AD	Beneficial effect in control of pruritus	100 or 300 mg daily orally administered for 6 weeks	Murata <i>et al.</i> , 2015
	<a href="#">Toreforant</a>	Phase IIa study in 162 patients with eosinophilic asthma	Failed to provide therapeutic benefit at the dose tested	30 mg once daily administration for 24 weeks	Kollmeier <i>et al.</i> , 2018
	Toreforant	Phase IIa study in 86 patients with active rheumatoid arthritis	Reduced signs/symptoms evaluated by the 28-joint Disease Activity Score-C-reactive (DAS28-CRP <sup>#</sup> ) protein through week 12	100 mg once daily orally administered for 12 weeks	Thurmond <i>et al.</i> , 2016
	Toreforant	Phase IIb study in 272 patients with active rheumatoid arthritis	No significant improvement in DAS28-CRP <sup>#</sup> protein through week 12	3, 10 or 30 mg once daily orally administered for 12 weeks	Thurmond <i>et al.</i> , 2016

AD, Atopic dermatitis; EDS, excessive daytime sleepiness; DAS28-CRP, 28-joint Disease Activity Score-C-reactive protein; mg, milligrams. Drugs and molecular targets conform to BJP's Concise Guide to Pharmacology (Alexander *et al.*, 2015).

<sup>#</sup> The DAS28-CRP is a Disease Activity Score, part of the many scores for rheumatoid arthritis (useful, reproducible and comparable assessment of the rheumatoid arthritis activity) (Prevoo *et al.*, 1995).



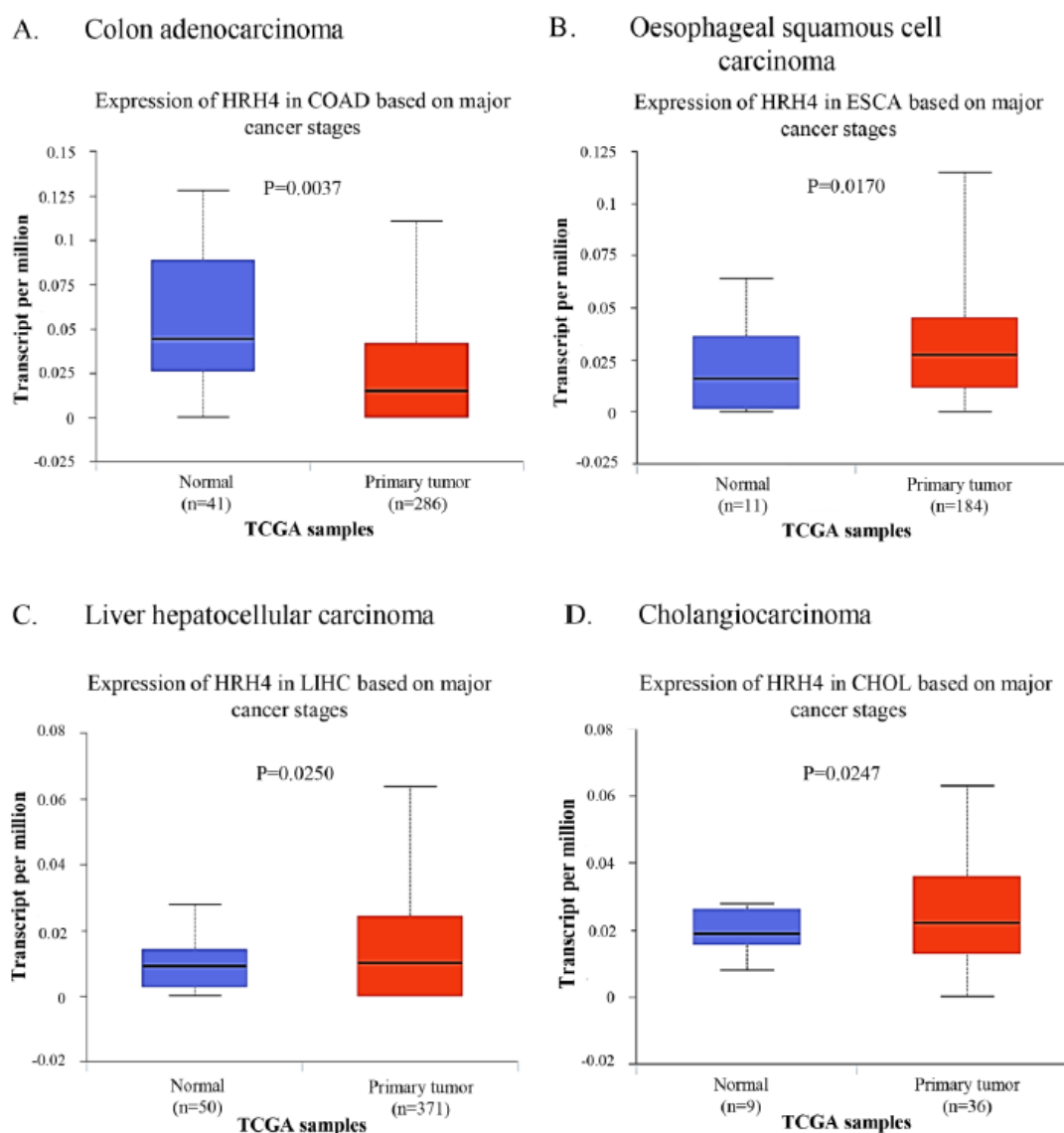
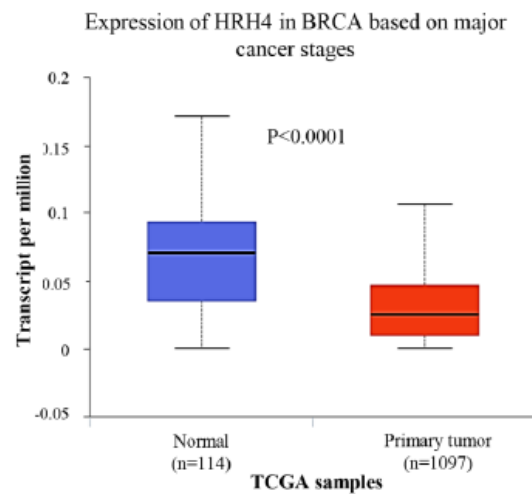


Fig 1

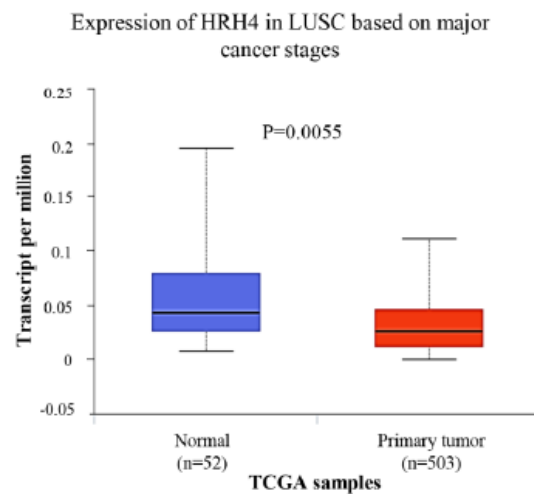
**Figure 1:** Boxplots generated in the UALCAN interactive web resource show relative expression of *HRH4* in transcripts per million (tpm) in normal tissue (blue box) and primary tumour (red box) samples. The samples used for the analysis are obtained from the genomic data of The Cancer Genome Atlas (TCGA) project. Boxplot showing relative expression of *HRH4* (A) in normal tissue (n=41, median: 0.044 tpm) and colon adenocarcinoma (COAD, n=286, median: 0.015 tpm) samples; (B) in normal tissue (n=11, median: 0.016 tpm) and

oesophageal squamous cell carcinoma (ESCA, n= 184, median: 0.027 tpm) samples; (C) in normal tissue (n=50, median: 0.009 tpm) and liver hepatocellular carcinoma (LIHC, n= 371, median: 0.01 tpm) samples; (D) in normal tissue (n=9, median: 0.019 tpm) and cholangiocarcinoma (CHOL, n= 36, median: 0.022 tpm) samples. T-test was performed using a PERL (Practical Extraction and Report Language) script with Comprehensive Perl Archive Network (CPAN) module “Statistics::T Test” (<http://search.cpan.org/~yunfang/Statistics-TTest-1.1.0/TTest.pm>) [(UALCAN web resource: <http://ualcan.path.uab.edu>.; Chakravarthi BVSK, *et al.* (2017)].

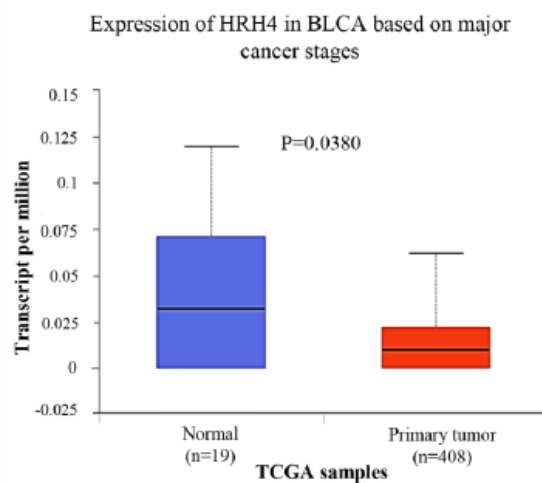
A. Breast invasive carcinoma



B. Lung squamous cell carcinoma



C. Bladder urothelial carcinoma



D. Uterine corpus endometrial carcinoma

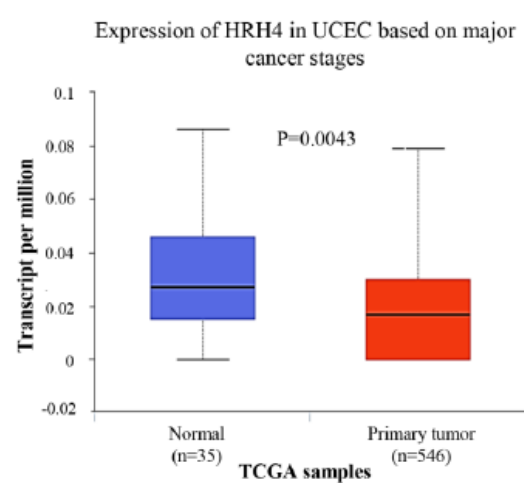


Fig 2

**Figure 2:** Boxplots generated in the UALCAN interactive web resource show relative expression of *HRH4* in transcripts per million (tpm) in normal tissue (blue box) and primary tumour (red box) samples. The samples used for the analysis are obtained from the genomic data of The Cancer Genome Atlas (TCGA) project. Boxplot showing relative expression of *HRH4* (A) in normal tissue (n=114, median: 0.07 tpm) and breast invasive carcinoma (BRCA, n=1097, median: 0.025 tpm) samples; (B) in normal (n=52, median: 0.043 tpm) and

lung squamous cell carcinoma (LUSC, n= 503, median: 0.026 tpm) samples; (C) in normal (n=19, median: 0.032 tpm) and bladder urothelial carcinoma (BLCA, n= 408, median: 0.01 tpm) samples; (D) in normal (n=35, median: 0.027 tpm) and uterine corpus endometrial carcinoma, UCEC (n= 546, median: 0.017 tpm) samples. T-test was performed using a PERL (Practical Extraction and Report Language) script with Comprehensive Perl Archive Network (CPAN) module “Statistics::T Test” (<http://search.cpan.org/~yunfang/Statistics-TTest-1.1.0/TTest.pm>) [(UALCAN web resource: <http://ualcan.path.uab.edu>.; Chakravarthi B VSK, *et al.* (2017)].

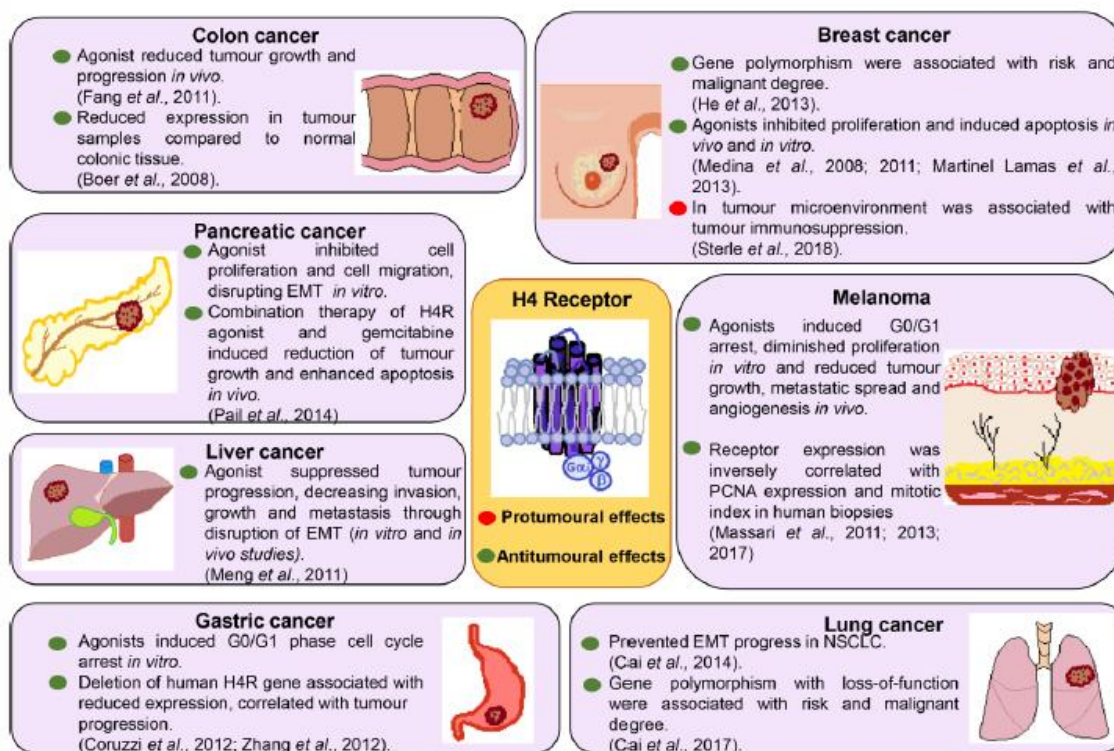


Fig 3

**Figure 3:** Main protumoural (●) and antitumoural effects (●) triggered by H4R in different types of cancer (EMT: epithelial to mesenchymal transition; KO: knock out; NK: natural killer cells; NSCLC: Non-small cell lung cancer).