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Targeting Oncogenic Receptor, Currently the Standard of Care

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Abstract

In 1989 - 91,George Zhu[1] first postulate oncogenic receptor (Voice of America, 1992, 12:31; Curr Pharm Biotechnol, 2013, 14:859 - 863), as a result of his experiments in which steroid PML-RARa fusion receptor gene rearrangement within t (15;17) translocation in acute promyelocytic leukemia (APL), and androgen cognating its (AR/ERa signaling or FGFR-1) receptor induced tumours of the breast glands in two aplastic anemia during the course of testosterone treatment (hormonal tumorigenesis). In the past 2 - 3 decades, there are at least 30 receptor genes involving in several of oncogenic process. These normal physiologic receptors linked to gene amplification, rearrangement, deletion and activating mutations, which converted receptor to oncogenic (also oncogenic receptor) in development, progressive and pathogenesis of benign and malignant diseases. Receptors included nuclear receptor family members (oncogenic estrogen/estrogen receptor alpha receptor/c-ros proto-oncogenic receptor, insulin and IGF-1 and -II/oncogenic IGF-1R, oncogenic PDGFAR, oncogenic TEL/PDGFRB, thrombopoietin (TPO)/TPO receptor, oncogenic MPL receptor, oncogenic androgen receptor, oncogenic pml/RARa, and GRβ); Oncogenic growth factor receptors (EGF/ oncogenic receptor EGFR, Neu oncogenic receptor, insulin receptor substrate 4 IRS4/insulin HGF/HGFR oncogenic signaling, met oncogenic receptor), Cytokine receptor rc family members (IL-2-BCM fusion, IL-3/oncogenic IL-3Ra, IL-7/oncogenic IL-7R and IL-21R-BCL6 fusion); Cytokine receptors including the βc family (G-CSF/oncogenic CSF3R, oncogenic EPOR), and oncogenic autocrine growth hormone/nuclear GHR and other VEGFR2. Upon ligand binding or external antigen stimuli, mutated growth factor receptors and mutant cytokine receptors including type I cytokine receptor may be activated via ligand binding receptor complex, receptor dimerizes especially receptor homodimerization, and induces transphosphorylation of tyrosine residues in the cytoplasmic domains which serves as docking sites for several adaptor molecular harboring SH2 domain or phosphotyrosine binding domain. These adaptor molecules recruit and activate downstream signaling molecules such as Ras/MAPK, phospholipase C-r, JAK-STAT molecules, NF-KB pathways through tyrosine- or serine/threnonine-phosphorylation. Among them, Ras /MAPK/ERK, PI3-K/akt and STAT pathways act as the major oncogenic signaling pathway. Overall, these receptors coupled with their ligands are key importance in human subtle balance in physiologically regulating multiple cellular processes, for example, in cellular proliferation and differentiation. Oncogenic receptors mutational activation and/or aberrant gene rearrangement are promiscuously interference with normal cell survival, anti-apoptosis and proliferation, and malignant initiation and progression. Others, in a special APL case, oncogenic pml/RARa fusion behave as a potent (constitutive) transcriptional repressor of RAR and retinoic acid signaling, inducing a differentiation blockage at promyelocytic stage which can be overcome with therapeutic doses of 9-cis retinoic acid or ATRA ligand (see in detail model, George Zhu, January 1991. Curr Pharm Biotechnol, 2013, 14: 849-858)[2,6,8]. This is the classical model of retinoic acid action. This encourages receptor normal agonist, and oncogenic receptor antagonists (or inhibitors) target therapy.

Keywords: Receptor; Oncogenic receptor; Gene activating mutation; Aberrant rearrangement; Tumours; Cancers

Introduction

Since introduction of oncogenic receptor concept by George Zhu from oncogenic pml/RARa fusion in etiology of a specific APL and androgen/androgen receptor oncogenic signaling in role of hormonal tumorigenesis in early 1989s[1-13], de The H and Chomienne C[14,15], at the same peroid, found that in t (15;17) APL the translocated retinoic acid receptor alpha (an RAR mutant) contribute to leukemogenesis. Neil JC[14-16] is in detail receptor-mediated leukaemogenesis from the oncogenic function of T cell antigen receptor (TCR oncogenic signal) on lymphoid cells not only bind external ligand but are crucial in cellular proliferation. In transgenic mice expressing a mutated TCRbeta lacking the variable chain (Detta V-TCRbeta) developed CD4+, CD8+, IL-2Ra positive T-cell lymphoma[17,18]. Patients with ataxia-telanglectasia are particularly prone to development of T-cell chronic lymphocytic leukemia with chromosomal abnormalities. The breakpoint is composed of a TCR J alpha chain region (from 14q11) fused to sequences derived from 14q32 but on the centromeric side of the IgCmu (IgH), indicating that a 14:14 translocation [t (14; 14) (q11; q32); inv (14) (q11; q32)] in the development of T-cell tumors[19,20]. Like mutated oncogenic growth factor receptors[21,22], antigen- independent B cell receptor (BCR) signaling drives the oncogenic process (Farinha, 2005). The genetic defects in heavy-chain disease (HCD) result in the production of abnormal membrane-associated heavy chain lacking an antigen-binding domain, these aberrant B-cell antigen receptors might engage in ligand-independent signaling, indicating a role in the genesis of HCD neoplasia[21-23]. Thus, BCR associated kinase inhibitors, such as ibrutinib, have revolutioned the treatment of chronic lymphocytic leukemia (CLL).

Yarden Y (1991)[24] propose neu oncogenic receptor from neu oncogene-related receptor tyrosine kinase (RTK), and this might be useful in neu oncogenic receptor[24-29] antagonists lapatinib and trastuzumab target therapy in metastatic breast cancer with HER2V659E mutation[30]. In a large trial of 48 HER2-positive early breast cancer patients, the adjuvant trastuzumab treatment demonstrates highly favorable outcome. Five-year overall survival rates and disease free survival rates were 95.8% and 93.8% respectively (Kato, 2015). Al-Nedawi[31] explore the area that microvesicles containing oncogenic receptor EGFRVIII released to cellular surroundings and blood of tumour-bearing mice,and can merge with the plasma membranes of cancer cells lacking EGFRVIII. This intercellular transfer of membrane-derived microvesicles (‘oncosomes’ -small plasma membrane buds,Robinson, 2008[32]) leads to the transfer of oncogenic activity including activation of MAPK and Akt and autocrine activation of its key signaling receptor (VEGF receptor-2), and increases in anchorage-independent growth capacity. Santos[33] studies oncogenic GRPR (gastrin-releasing peptide receptor) in neoplastic multiple signaling pathway. Somatic mutations in cholecystokinin 2 receptor (CCK2R) alter receptor activity that promote oncogenic phenotype, and the importance of evaluating CCK2R inhibitors to block mutant forms of this receptor[34]. Intriguing, epithelial cell adhesion molecule (EpCAM), as a homophilic adhesion protein,is a novel oncogenic receptor which frequently overexpressed in epithelia, progenitors, embryonic stem cells, carcinoma and cancer-initiating cells, and target its antibodies[35]. The present will in brief focus on recent innovative diagnostic and therapeutic strategies forthcoming in this area.

Steroid hormone receptors oncogenic signaling

Steroid hormones are a biologically related hormones secreted into blood stream by the adrenal cortex and glands (ovaries and testes) (Singh and Kumar, 2005). After releasing into the blood, steroid hormones enter target cells by crossing the cytoplasmic membrane and exert their action by binding to high affinity receptors, also known as steroid hormone receptors. Steroid hormones control a wide variety of cellular function. Sex hormone (androgen and estrogen) play an important role in gonadal (sex determination) development, the formation of the menstrual cycle. At puberty, estradiol induces mammary duct formation. As the hypothalamic-pituitary-ovarian axis matures, there is a brief phase of anovulatory cycles during which the mammary gland is influenced principally by estrogens. Once ovulation is established, corpus luteum produces progesterone, which stimulates growth of the lobular velour structures. During the reproductive years, progesterone promotes differentiation of alveolar cells into secretory cells, and dilation of the duct system. In conjunction with prolactin and other metabolic hormones, progesterone stimulates lipid droplet formation, and secretory activity. While prolactin and growth hormone are the most important pituitary hormones affecting growth of the mammary gland during pregnancy. It is estradiol and progesterone that prevents the full expression of these secretory effects on the mammary epithelium. At parturition, the sudden withdrawal of these two hormones permit the breast to respond to the lactogenic hormones. Progesterone can acts in synergy with estradiol to prime the mammary gland to respond to mitogens like prolactin, glucocorticoids and growth hormone, which is essential for human alveolar gland development and growth (Horwitz, 1985). The following figure 1 represents hormone biosynthetic reaction.

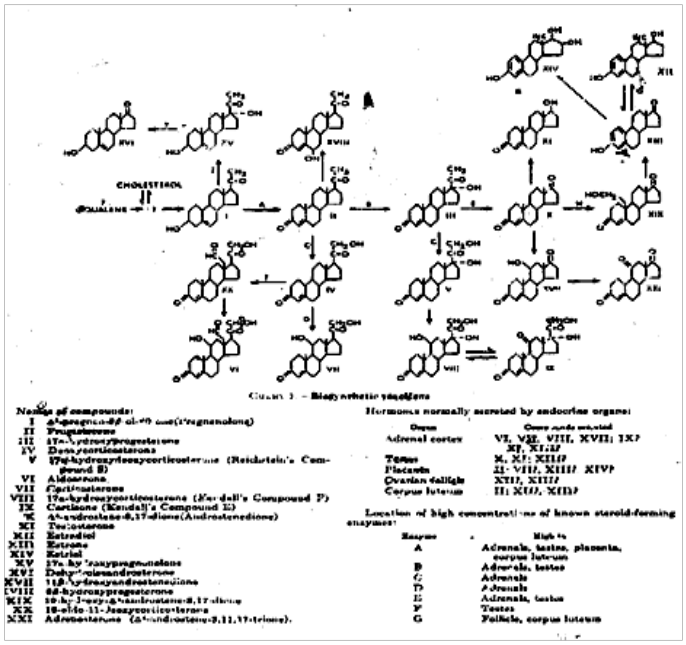
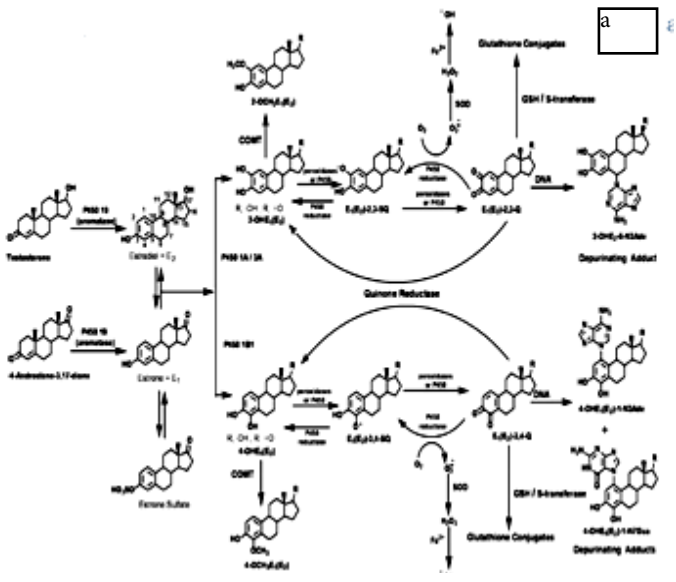


Figure 1: Hormones normally biosynthetic reaction.

The estrogen receptor (ER) is found in a wide variety of species and is involved in the programming and regulation

of gene expression in vertebrate female sex-accessory tissue[36]. Estrogen E2/ERa signaling plays an important role in the regulation of mammary gland development and function,and also contributes to the onset and progression of breast cancer. More than 70% of human breast cancers express ERa, and elevated levels of ERa in benign breast epithelium correlate with increased risk of breast cancer[37]. Green S & Chambon P (1986)[38] described oncogenic hormone receptor from human oestrogen receptor cDNA sequence. This carcinogenicity of estrogen is attributes to receptor-mediated stimulation of cellular proliferation.Increased proliferation could result in turn in accumulation of genetic damage and stimulation of the synthesis of growth factors that act on the mammary epithelial cells via an autocrine or paracrine loop[39]. There were evidence that estrogen-dependent cell line (MCF-7) cells under estradiol (E2) stimulation release some known polypeptide growth factor activities (EGF-like, IGF-1-like)[40]. Dickson RB and Stancel GM (2000)[41] discuss estrogen receptor-mediated processes in normal and cancer cells. ER-mediated regulation of gene expression plays many significant roles in normal and cancer cells and this will improve the understanding of hormonal carcinogenesis.

Furthermore, Russo (2009)[42], Santen, Cavalieri, Rogan (2009)[43] and Yager, Yue (2013)[44-46] discussed estrogen receptor-dependent and independent mechanisms of breast carcinogenesis. ERa mediated stimulation of breast cell proliferation with a concomitant enhanced rate of mutations, and estradiol metabolites (see figure 2a) to genotoxic DNA mutation cause DNA damage (figure 2b). Thus, ERa function as estrogen activated transcription factor and involved in the stimulation of estrogen target genes in the regulation of cell cycle progression and growth of breast epithelium[47]. As Clarke described[48], some ERa/PR-positive epithelial cells are quiescent breast stem cells that acts as 'steroid hormone sensors'. Such hormone sensor cells are likely to secrete positive or negative paracrine/ juxtacrine factors dependent on the prevailing estrogen or progesterone concentration to influence the proliferative activity of adjacent ERa/PR-epithelial cells. This might represent one step toward the development of neoplasia and malignancy-invasive tumors.



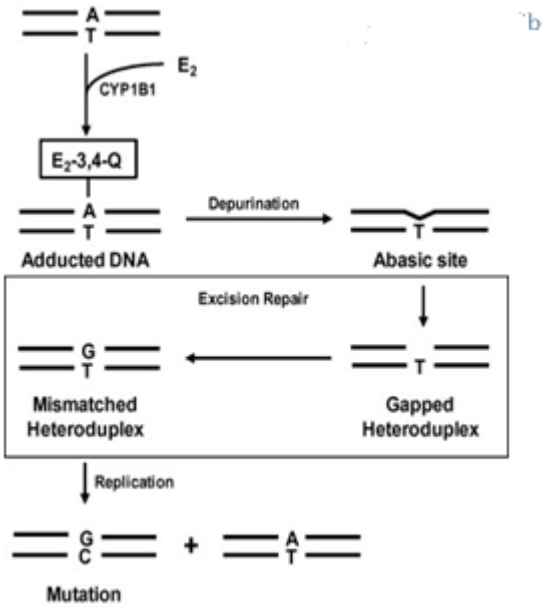


Figure 2: a. Estradiol metabolites reaction. b). Schematic description of DNA damage mutation following formation of depurinating adduct. (Data adapted from Yue & Yager, et al, Steroid, 2013, 78:161-70[35]).

Utilizing ERKO/wnt-1 oncogene mice[49]. (figure 3) and aromatase/ERKO transgene mice[50], they demonstrated the role of ERa-dependent in mammary development and carcinogenesis. Lack of ERa mice results in impaired mammary development and much delayed tumor incidence even in the presence of tissue estrogen (50% of mammary tumors at 5 months in ER-positive animals versus 11 months in those without ERa). Whereas introduction ERa into the tTA/TAg mice[51] and DES-treated MT-mER transgene mice[52,53] developed mammary adenocarcinoma (at 8 months) and preneoplastic lesion atypical hyperplasia (at 4 months), which implicate that ERa contributes to carcinogenic through ER-mediated signal transduction, increasing estrogen-responsive cell proliferation, and ERa signaling in mammary cancer initiation and progression.

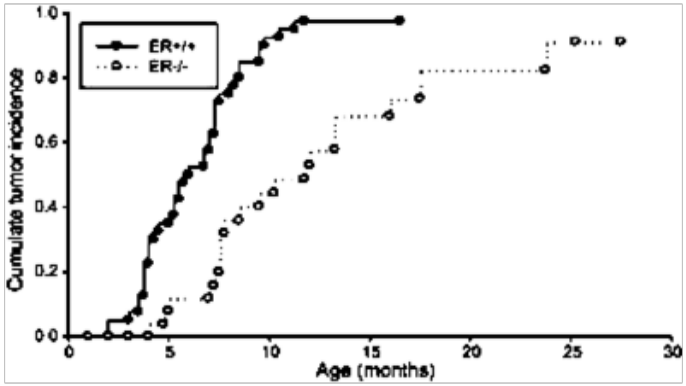


Figure 3: The effect of estrogen receptor alpha (ERa) on the development of mammary tumors in Wint-1 transgenic mice. (Data adapted from Bocchinfuso, J Mamm Gland Biol Neoplasia, 1997, 2:323-34[49]).

Moreover, mutations in estrogen receptor converted estrogen receptor-dependent breast tumor into estrogen-independent growth[54]. Fuqua (2000)[55] found a K303R estrogen receptor alpha (ERa) mutation in human premalignant breast lesions (see figure 4). The K303R mutation formed tumors in nude mice

faster than cells expressing wild-type ERa in the presence of low levels of estrogen (at 10 - 12 M estradiol), and those K303R ERa-expressing tumors are estrogen-independent growth[56]. From screeing of those ER+ breast cancer, Veeraraghavaa and colleagues[57,58] detected oncogenic ESR1- CCDC170 fusion positive tumors. This neoplastic ESR1-CCDC170 fusion leads to anchorage- independent growth, reduced endocrine sensitivity and enhanced xenograft tumor formation, suggesting a new concept of this oncogenic receptor ESR1 fusion in path biology in a more aggressive subtype of breast cancer.

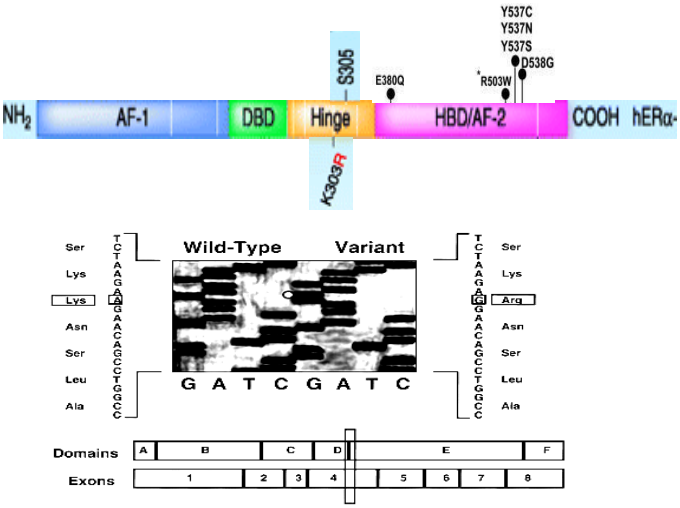


Figure 4. Sequence analysis of ER Var and WT cDNAs isolated from frozen breast hyperplastic tissue. A portion of the sequencing products is shown for WT and Var clones, demarcating the location of the G transition and Arg substitution. ER domains A–E and the exons across these domains are shown on the bottom, with the location of the Lys-to-Arg change demarcated with a box across exon 4 at the end of domain D (Data adapted from Fuqua, et al, Cancer Res, 2000, 60:4026-9[55]).

Thus far, in addition to tamoxifen and fulvestrant, AZD9496,a non-steroid small molecule inhibitor of oncogenic (or neoplastic, due to not targeting a normal ERa) ERa[2-6,38,51,52,59], bound and down- regulated clinically relevant ESR1 mutants in vitro and inhibited tumor growth in an ESR1 mutant patient-derived xenograft model that included a Y537 and D538G mutation[60,61]. AZD9496 is currently being evaluated in a phase I clinical trial[62].

Using heterotypic tissue recombination, Cunha (1981-2008)[63] established a stromal androgen receptor for mesenchymal-epithelial transition (EMT) in normal androgen-dependent prostate development and in the etiology of benign prostatic hyperplasia[64]. By different methods including immortalized human prostate cells expressing androgen receptor[64] and androgen receptor transgene[65], they demonstrated that androgen receptor is oncogenic,and this oncogenic receptor induces prostate intraepithelial neoplasia (PIN) and plays a cruical role in transforming process in prostate cells. The AR-expressing PrECs are dependent on circulating testosterone for tumor growth, and immortalized PrECs lacking AR failed to form tumors. But this androgen receptor is difficult to characterize as an oncogene[64]. Mononen (2000)[66] and Koivisto (2004)[67] detected the R726L mutation of androgen receptor (AR) in Finnish patients with sporadic or familial prostate cancer, which may confer an up to 6-fold increased risk of a small fraction of prostate cancer in Finlan. T877A mutation of AR was identified in LNCaP cell line and metastatic cells of androgen -independent prostate cancer[68-74], whereas V739M was identified in early stage PCa[75]. Nyquist (2013)[76] discovered intragenic AR gene rearrangements in CRPC tissues, rendering expression of truncated AR variants proteins lacking the AR ligand-binding domain, constitutive activity of AR, and intragenic ARv567es cDNA formed tumor faster rate and a CRPC growth independent of full-length AR or androgens. Therefore, targeting oncogenic AR variants[7,64,77-82] (here, please note that it is no need to target a normal AR) includes AR antagonists bicalutamide and enzalutamide, which might provide an approach to suppress prostatic intraepithelial neoplasia (PIN) development. In phase II trials, the CBR (clinical benefit rate) of 19% was observed with bicalutamide 150 mg daily dose in selected patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer[83].

In another area,increased thyroid diseases and thyroid papillary carcinoma(PTC) associated with a high dietary iodine intake[7,84-93].

GRß/STAT-5 pathway was found to be involved in erythrocytosis[94], and GR/SGK1(including GR-SGK1-FOXO3a signaling pathway and GR-SGK1-MKP1/DUSP1 pathway) network linked to higher tumor grade and antiapoptotic and increased cancer recurrence[95-97]. Moreover, the aberrant glucocorticoid receptor signaling in breast cancer[98-101], prostate hyperproliferation[97,102,103], Cushing's disease[104] and Nelson's syndrome[105]. Thus, GR activation is sufficient to provide a potent signal for cell survival in mammary epithelial cells.Induction of serum and glucocorticoid-regulated kinase-1 (SGK-1) expression is required for GR-mediated epithelial cell survival signaling. SGK-1 is a direct GR target and encodes a serine-threonine kinase with significant homology to Akt-1. In immunohistochemical analysis, nucleus GR-immunostaining and glucocorticoid receptor (GR)- immunopositive cells were abundantly present in subclinical Cushing's disease due to pituitary adenomas (2 macroadenomas and 8 microadenomas), suggesting impaired glucocorticoid action, at least in part, in tumorigenesis of this disease[104]. RU486 (mifepristone), a glucocorticoid receptor antagonist, has been successful treatment of the Cushingoid phenotype with markedly elevated lymphocyte glucocorticoid receptor numbers in a transient Cushing's syndrome[106]. Mifepristone may also be a useful strategy for increasing tumor cell apoptosis in chemotherapy-resistant GR+ triple- negative breast cancer (TNBC)[108]. In addition, the cortisol/cortisone-responsive AR (AR (ccr)) has two mutations (L701H and T877A) that were detected in the MDA PCa human prostate cancer cell lines established from a castrated patient whose metastatic tumor exhibited androgen-independent growth. GR antagonist RU38486 showed inhibitory activity[102], but its therapeutic application to treat prostate cancer may be limited. Thus, the combination of ARccr receptor antagonists bicalutamide (casodex) together with a ligand suppressor (triamcinolone) represents a new therapeutic strategy for the treatment of the subset of androgen-independent prostate cancers harboring the L701H or ARccr type.

So fathered is a conflict among hormone FSH/FSH receptor in etiology of epithelial ovarian cancer[109,110]. Actions of FSH (follicle-stimulating hormone) in reproductive physiology are essential for folliculogenesis and steroidogenesis[111], FSH receptor (FSHR), a transmembrane receptor with a G protein-coupled signaling, is expressed by granulosa cells in developing ovarian follicles. Over expression of FSHR activates on-

cogenic pathways through FSHR-induced EGFR amplification, and HER-2/ neu and activated ERK1/2 in preneoplastic immortalized ovarian surface epithelial (IOSE) cells[112]. The data by epidemiological studies that an increased occurrence of ovarian cancer has been suggested with exposure to high levels of gonadotropins during post menopause or infertility therapy[113-115].

Retinoid can regulate proliferation and differentiation of normal myeloid cells, and that supraphysiological levels of retinoic acid (9-cis RA or all-trans RA) can induce abnormal promyelocytes toward maturation. These leukemic cells harboring steroid PML-RARA translocation play a central role in etiology of APL[8,12,13,116]. The PML-RARa chimera can function as a strong transcriptional repressor of retinoic acid (RA) signaling and RAR function by perturbing normal retinoid signaling, leading to a block in differentiation and in an accumulation of leukemic cells at promyelocytic stage[8,10,116-129] (see model, figure 5, George Zhu, 1991, 2013 - 2014). This oncogenic receptor is locked in its "off" regulated mode thereby constitutively repressing transcription of genes or key enzymes that are critical for differentiation of hematopoietic cells[8,130]. Moreover, the PML-RARa apparently involved in part the defects in ability to release corepressor under physiological hormone concentration, the wild-type RARa readily form heterodimer with the retinoid X receptors (RXRs). In contrast, chimeric pml/RARa oncoprotein exhibited an enhanced ability to bind to DNA as homodimer. This enhanced homodimerization by RAR chimeras implicates in aberrant co repressor interaction properties of these oncogenic receptor derivatives, influences their DNA recognization, and appears to prevail in neoplastic cells of these oncoproteins[130]. These differences in target gene recognition by the normal and oncogenic RARa protein may contribute to the leukemogenic phenotype[130].

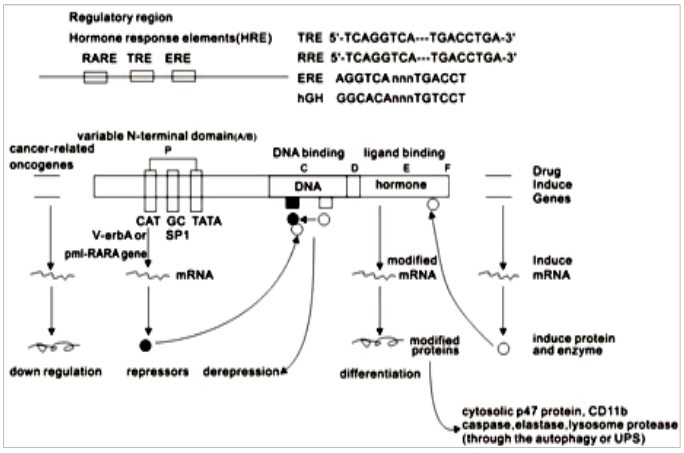


Figure 5. Hypothetical model of the regulation of retinoic acid (RA) action (George Zhu, January 1991, revised in 2012). Schematic alignament of the receptor protein. The two highly conserved regions, identified as the putative DNA- binding (C) and hormone -binding (E), ahinge region (D) and the non- conserved variable NH2-terminus (A/B) as described above. (Data adapted from George Zhu, January 1991. Curr Pharm Biotechnol, 2013, 14:849 - 858[4,5]).

Targeting oncogenic growth factor receptors

The EGF receptor (EGFR)[130] has a key role in normal embryonic development, adult tissue hemeostasis and many pathological processes, particular tumor formation. Aberrant EGFR activation becomes oncogenic due to over expression and/or amplification of the EGFR gene or by autocrine / paracrine growth factor loops, whereas activating dimerized mutations promote EGFR signaling, which lead to ligand-independent[130-133]. Phosphorylation of this oncogenic receptor at residues Tyr845, Tyr1045 and Tyr1173 leads to receptor activation and downstream signaling[135,136]. Oncogenic receptor EGFR[2-6,9,11,134,137-139] was found to involved in A431 human carcinoma cells[140-143], squamous cell carcinoma (SSC)[144], epithelial cell lines from mammary carcinoma[145], glioblastoma stem cells[9,146,147], EGFR+++ positive in one glioma, George Zhu, 2013], and colorectal carcinoma tissue[148]. Oncogenic EGFR mutations are found in 10% to 35% of lung adenocarcinomas, with predominant in a subset of patients with non-small cell lung cancer (NSCLC)[149-151]. These mutations, which commonly occur as either small in-frame deletions in exon19 or point mutations T790M and L858R in exon21 within the EGFR tyrosine kinase domain, confer constitutive activity and sensitivity to EGFR tyrosine kinase inhibitors(TKI)[152,153]. Recent, Gallant[152] identified a novel EGFR alterations in lung cancer: EGFR exon 18-25 kinase domain duplication (EGFR-KDD). EGFR-KDD is oncogenic and oncogenic EGFR-KDD-transformed cells are sensitive to the EGFR TKI afatinib. Konduri and colleagues[153] reported five patients with metastatic lung cancer whose tumors harbored EGFR fusion, most commonly RAD51, are recurrent in lung cancer. Four of whom were treated with EGFR TKI erlotinib with documented antitumor response for 5, 6, 8, and 20 months respectively. These patients whose tumors harbored EGFR fusions are oncogenic in preclinical studies. In mouse model, transgenic mice expressing EGFR L858R in type II pneumocytes developed atypical adenomatous hyperplasia and multifocal adenocarcinoma, and gefitinib inhibited tumorigenesis completely[154]. Blesa[155] present a durable complete remission of a relapsed glioblastoma with a complete radiologic response and the combination of cetuximab and bevacizumab in a third-line setting, that has offered a progression-free survival of 20 months. In Cuba, CimaVax-EGF, promising, an active vaccine targeting EGF as the major ligand of EGFR, it is in use as a cancer therapy against non-small-cell lung cancer (NSCLC) [156,157].

PDGFRa mutations are oncogenic (tumorigenic) and developed 100% of mice with brain tumors whereas only one of 19 mice implanted with cells over expressing wild-type PDGFRa developed into brain tumor *in vivo*[158,159]. This D842V mutant was effectively inhibited by crenolanib, a specific inhibitor of PDGFRa and PDGFRß. Golub (1994)[160] identified that PDGF receptor ß is oncogenic in pathogenesis of chronic myelomonocytic leukemia with t (5;12) chromosomal translocation, targetable oncogenic receptor tyrosine kinases PDGFRa/PDGFRß, and FGFR fusions[145-147] in diverse cancers have made some major progress. For example,these hypereosinophilia (HES) patients with FIP1L1/PDGFRA have excellent responses to imatinib treatment[167-172]. At present, Imatinib, a selective inhibitor of ABL, KIT, and PDGFRA/B, is the first line target therapy for gastrointestinal stromal tumor (GIST)[173].

Hepatocyte growth factor (HGF), like other growth factors, has different effect in different cells. HGF regulates cell growth, cell mortality and morphogenesis by acting a tyrosine signaling cascade after binding to the proto-oncogenic receptor for HGF (HGFR, also proto-oncogenic receptor c-met, met receptor)[174-177]. HGF enhances hepatocyte growth, potently suppresses apoptic death of hepatocytes and decreases serum bili-

rubin and serum ALT (alanine aminotransferase), which provide therapeutic action of HGF, including severe hepatitis, falminant hepatic failure[178] and liver cirrhosis[179].

HGF-HGF receptor (met oncogenic receptor) signaling stimulate growth of mouse C127 cells transformed phenotype[180], Caki-1 (a human kidney clear cell carcinoma cell line), U87-MG (a glioblastoma cell line)[181], canine osteosarcoma cells[176], and human hepatoblastoma cells[181], and AML[182].

In vitro HGF can transform immortalized mouse liver epithelial cells[183]. Serum HGF levels are elevated in patients suffering from chronic hepatitis and liver cirrhosis (Tomiya, 1992). Moreover, hepatocytes from transgenic mice expressing HGF grew more rapidly than did those from normal siblings. *In vivo*, Fao HGF cells produced tumors when transplanted into nude mice[184]. These conditions cause persistent hepatocellular damage and regeneration; consequently, there are associated with the subsequent of hepatocellular carcinoma (HCC). Thus, HGF-HGF receptor signaling might play an important role in carcinogenesis[182,185]. PRS-110 (starting at 0.8 mg/kg and going up to 30 mg/kg) specifically binds to Met receptor with high affinity and blocks HGF interaction on ligand-dependent (U87-MG) and ligand-independent (Caki-1) xenograft model[181]. Animals were randomized for the treatment with a novel met inhibitor EMD1214063 (50 mg/kg/d), which resulted in a complete regression of the sensitive H1112L met variant-derived tumors[186]. Foretinib, the first multi-target c-met TKI to under clinical investigation, produced a promising benifit in HCC patients[163]. Recently, the chemically-modified monovalent antibody DN30 was found to inhibit ligand- independent activation of the met oncogenic receptor, providing an another target therapy[187-189].

Cytokine receptors had oncogenic mutant variants in cancer

Growth hormone (GH)/oncogenic GH receptor (GHR) [190-193] was associated with growth hormone receptor deficiency[194]; gigantism, acromegaly and cancer risk[195-199]; GHR determines 'cancer- like' features[193]. And GH-releasing hormone GHRH/GHRH receptor oncogenic signaling[201,202]. Insulin/insulin receptor/Ros proto-oncogenic receptor homologue, and IGF-I, IGF-II/ oncogenic receptor PTK IGF-IR linked to physiology and diseases (short status, oncogenic transformation process)[202-209]; and IGF-I (Mecasermin) replacement therapy[212-214]. Interesting, the oncogenic mechanism in Ewing sarcoma harboring oncogenic EWS/NR4A3 fusion involves a novel pro- oncogenic IGF/IGF-1 receptor signaling pathway including post-transcriptional derepression of IGF signaling by the EWS/Fli1 fusion oncoprotein via miRs[215], and this provide therapeutic targeting anti-IGF-1 receptor antibody in Ewing Sarcoma[216-218]. G-CSF (filgrastim) has been used in clinic for more than 2 decades to treat congenital and acquired neutropenias[219-224]. It is highlight the clinical application of G-CSF to children with severe congenital neutropenia (SCN) and especially in patients with neutropenia harboring in the G-CSF receptor (CSF3R) gene, which is correlated to an increased risk for development of MDS and acute myeloid leukemia(AML)[225]. There are two classes of CSF3R mutant variants:truncations of the cytoplasmic domain[226,227] and membrane proximal point mutations including T618I[228]. Truncated CSF3R mutations are the mutant type nearly almost observed in SCN and abnormal signaling of this oncogenic receptor variants in malignant transformation, whereas membrane proximal mutations (particularly T618I) are the predominant mutation type observed in chronic neutrophilic leukemia (CNL) and atypical (BCR-ABL negative) chronic myeloid leukemia (aCML), and confer ligand-independent growth[228]. Maxson and colleagues[229] identified activating mutations for CSF3R in 59% (16/27) of patients with CNL or atypical CML. *In vivo*, the activating mutation in the CSF3R gene induces hereditary chronic neutrophilia[230]. Mice transplanted with CSF3R T618I-expressing hematopoietic cells developed a myeloproliferative disorder[228]. Treatment with the JAK inhibitor ruxolitinib lowered the white blood cells and reduced spleen weight. These results indicate that activating mutant CSF3R is oncogenic[229] and sufficient to drive a myeloproliferative disorder resembling CML and CNL that is sensitive to pharmacologic JAK inhibition[228].

Another more example is that a translocation t (14; 19) (q32; P13) was involved IGH@ and the cytokine receptor EPOR at 19P13 in two patients with B-cell precursor acute lymphoblastic leukemia (BCP-ALL)[231-233]. An over 230- and 241-fold increase in the expression of EPOR were observed in 2 patients at diagnostic and relapse samples respectively. The EPOR-IGH/IGK chain fusions result in truncation of the cytoplasmic tail of EPOR at residues similar to the mutant EPOR in PFCP, with preservation of the proximal tyrosine essential for receptor activation and loss of distal regulatory residues. Expression of truncated EPOR in mouse B cell progenitors induced ALL *in vivo*. The data implicate oncogenic erythropoietin receptor in role of both benign erythrocytosis and malignancy[234,235]. Moreover, mutation of erythropoietin receptor (EPOR) gene was associated with primary familial and congenital polycythemia (PFCP). Truncated mutations of 59 to 84 amino acids of EPOR at c-terminus lead to loss of the intracellular cytoplasm tail of the receptor, and prolonged proliferative signal resulting in hypersensitivity (5-10 fold increased sensitivity) to erythropoietin, and prolonged activity of JAK2 kinase and STAT5 activity[236-239]. The leukemic cells with oncogenic EPOR fusions were sensitive to JAK-STAT inhibition, suggesting a therapeutic option in high-risk ALL.

Accumulated studies, constitutive activation of cytokine interleukin-2 (IL-2) gene can induce autocrine growth of IL-2-producing leukemic cells in adult T-cell leukemia[240], *in vitro* transformation and tumorigenicy of T cells[241-244], and tumour cells bearing IL-2-BCM fusion in a T cell lymphoma with t(4;16)(q26;p13) translocation[245]. IL-2 binds to IL-2 receptor a (IL-2Ra) and rc subunit of the IL-2 receptor (IL-2RG) sharing with other cytokine receptor super family (including IL-7 receptor, IL-21 receptor) that receptor complex transduces growth and differentiation signals[246]. Under physiological condition, IL-2 appears to act on antigen-specific proliferation of T lymphocytes, immune thymocytes, B-lymphocytes, natural killer cells (NK cells) and lymphokine-activated killer cells (LAK cells), which linked to adoptive immune therapy[247].

In vitro nude mice, fibroblasts transfected with a chimera molecule containing the extracellular IL-2 binding domain of the IL-2R cDNA and the transmembrane and intracellular kinase domain of the EGF receptor cDNA, were morphologically transfomed and produced rapidly growing tumor[248]. Moreover, retroviral expression of IL-2RG restore signaling by IL-7 receptor to X-SCID precursor cells in T-cell progression to the pro-leukemic effects of ectopic LMO2[249]. Recently, the chromosomal translocation t (5;9) (q13; q22) in peripheral T cell lymphoma

generating the interleukin 2 inducible T cell kinase (ITK)-spleen tyrosine kinase (SYK) fusion kinase mimics a T-cell receptor signal and drives oncogenesis in mouse models (Pechloff, 2010).

Activation of the interleukin-3 (IL-3) gene by the enhancer of the IgH fusion leads to the overexpression of IL-3 gene product in 2 cases of acute lymphocytic leukemia with t (5; 14) (q31; q21) translocation[250]. Serum IL-3 correlated with the clinical course. When the patient's leukemic cell burden was highest (WBC 116,500/ul, lymphoblasts 33,785/ul), the serum IL-3 level was highest (799,5 pg/ml); whereas complete remission (WBC 123,00/ul, lymphoblasts 0/ul), serum IL-3 levels decreased to 105,1 pg/ml. Therefore, overexpression of IL-3 gene coupled with the presence of aberrant IL-3 receptor in these cells could account for oncogenic effects of proliferatative advantage and may play a central role in the pathogenesis of leukemia[250,251]. Aberrant presence of cystiene residues was shown to induce homodimerization of mutant interleukin-7 receptor (IL-7R), which drive constitutive signaling via JAK1 and independently of IL-7, rc or JAK3[252], promoting cell transformation. This abnormality is involved in -10% human pediatric T-cell leukemogenesis, paving the way for therapeutic targeting oncogenic IL-7R-mediated signaling in T-ALL[253-255]. Interleukin-21 receptor (IL-21R) is capable of signal transduction through homodimerization or potentially heterodimerization with IL-2R gamma. IL-21 and IL-21R not only regulates proliferation of mature B cells and T cells in response to activating stimuli but also mediate expansion of NK population from bone marrow. The gene for IL-21R is found the partner of BCL6 in t (3; 16) (q27; p11), which is recurrently observed in diffuse large B-cell lymphoma and a lymphoma cell line YM[256]. This IL-21R/BCL6 fusion gene is clearly associated with lymphoid cell origin.

Conclusion

To date, antibodies that target oncogenic receptors are often targeted toward lysosome[257] or blockade of translocation from the endoplasmatic reticulum to the cell surface of specific antigens such as vascular endothelial growth factor receptors (VEGFR2) or Tie2[258]. For instance, targeting cells with biotinylated ligands and addition of streptavidin efficiently targets trastuzumab to lysosome and this crosslinking of trastuzumab increased lysosomal degradation of its cognate oncogenic receptor Her2 in breast cancer cell lines[257]. Another burgeoning class of targeted chemotherapies called antibody-drug conjugates (ADCs). This ADCs that have demonstrated sufficient efficacy to gain and retain clinical approved are ado-trastuzumab emtansine(brand name Kadcyla) and brentuximab vedotin (brand name Adcetris)[259]. The auristatin-based antibody-drug conjugate BAY1187982 is for the treatment of FGFR2-positive solid tumors[195]. Another, the nicotinic acetylcholine receptor a7-nAchR (toxicology) is the oncogenic receptor, which mediated nicotine (NNK and NNN) oncogenic signaling in an important role in the initiation and progression of cancer including lung cancer and this oncogenic response was in parallel with the mutagenic and cytotoxic effects of tobacco smoke to promote the growth and angiogenesis of the tobacco related cancers[260].Thus nAchRs yiel- new targets for the prevention and treatment of tobacco related cancers. Thus, down regulating oncogenic receptors may be useful paradigm and perspective in currently the third-line setting of clinical target therapy and cancer biology (Woodman, 2016; George Zhu, 2014).[261]

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