Cellular and Molecular Mechanisms Implicated in the Dual Role of ROR2 in Cancer

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Abstract

The Wnt pathway plays an essential role in the initiation and progression of various types of cancer. ROR1 and ROR2 are Wnt receptors that are critical for β-catenin-independent (non-canonical) pathways and have been linked to processes driving tumor development and progression, such as cell proliferation, survival, invasion, and therapy resistance. Both receptors have garnered interest as potential therapeutic targets since they are largely absent in adult tissue, are overexpressed in several cancers, and, as members of the receptor tyrosine kinase family, are easier to target than all other components of the pathway. Unlike ROR1 which always promotes tumorigenesis, ROR2 has a very complex role in cancer acting either to promote or inhibit tumor progression in different tumor types. In the present article, we summarize the findings on ROR2 expression in cancer patients and its impact on clinical outcome. Further, we review the biological processes and signaling pathways regulated by ROR2 that explain its dual role in cancer. Finally, we describe the ongoing strategies to target ROR2 in cancer.

Keywords

ROR2, cancer, oncogene, tumor-suppressor gene.

Abstract

ROR1 and ROR2 are Wnt receptors that are critical for β-catenin-independent Wnt pathways and were have been linked to processes driving tumor progression, such as cell proliferation, survival, invasion, and therapy resistance. Both receptors have garnered interest as potential therapeutic targets since they are largely absent in

adult tissue, are overexpressed in several cancers, and, as members of the receptor tyrosine kinase family, are easier to target than all other components of the pathway. Unlike ROR1 which always promotes tumorigenesis, ROR2 has a very complex role in cancer acting either to promote or inhibit tumor progression in different tumor types. In the present article, we summarize the findings on ROR2 expression in cancer patients and its impact on clinical outcome. Further, we review the biological processes and signaling pathways regulated by ROR2 that explain its dual role in cancer. Finally, we describe the ongoing strategies to target ROR2 in cancer.

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1. Introduction

An important feature of cancer is the reactivation of developmental pathways that are critical for embryogenesis. One example is the Wnt signaling pathway. This pathway is complex and includes a vast diversity of ligands, receptors, and molecular mechanisms activated after ligand-binding [1,2]. Among Wnt receptors, there are three members of the Receptor Tyrosine Kinase (RTK) family, ROR1, ROR2, and Ryk, which play an important role in early embryonic development. During advanced gestation, their expression is negatively regulated and becomes virtually undetectable in most adult tissues. However, its aberrant expression has been described in certain pathologies, including various types of human cancer [3-5]. ROR1, for instance, is over-expressed in several tumor types and was associated with pro-tumorigenic features. In contrast, ROR2 appears to have a dual role in cancer, being able to act either as a repressor or as a promoter of cancer progression depending on the tumor type [6]. In either case, ROR2 has become a relevant protein in cancer, either as a prognosis marker or as a promising therapeutic target. In this review, we will summarize current insights into the dual role of ROR2 on cancer and will describe the various cellular processes and signaling pathways regulated by this receptor and its potential use as a therapeutic target.

2. Wnt signaling

The human Wnt family consists of 19 secretory glycoproteins that are highly conserved, particularly on its consensus sequence of asparagine [7]. The glycosylation and palmitoylation of Wnt proteins are of great importance due to their implication in the correct folding, secretion, and biological activity [8,9]. Wnt signaling regulates fundamental cellular processes such as cell fate determination and organogenesis during embryonic development, normal adult tissue homeostasis, motility, polarity, and stem cell renewal [10,11]. Once secreted to the extracellular space, Wnts can bind to different kinds of receptors and co-receptors, including proteins from the Frizzled (Fzd) family, low-density lipoprotein receptor-related proteins 5 and 6 (LPR5/6), orphan tyrosine kinase-like receptor 1 and 2 (ROR1/2), and related receptor tyrosine kinase (Ryk). Wnt ligands interact with their receptors in an autocrine or paracrine way, triggering various types of cellular responses that are classified into canonical (or β-catenin-dependent) and non-canonical (or β-catenin-independent) pathways [12,13]. The activity and function of Wnt ligands depend both on the cellular context and on the ligand-receptor pairing, which determines the activated downstream pathway. Generally, Wnt1, Wnt3a, and Wnt8 activate the

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β-catenin-dependent pathways, while Wnt4, Wnt5a, and Wnt11 triggers β-catenin-independent pathways [1,14,15].

In the canonical pathway, binding of Wnt ligands to their receptors (Fzd and LPR) results in activation of cytoplasmic Dishevelled protein (Dvl), leading to Axin dephosphorylation and a decline of its cytoplasmic content resulting in the inhibition of the β-catenin degradation complex. As a result, β-catenin can accumulate and translocate to the nucleus where it enhances T cell factor/lymphoid enhancer factor (TCF/LEF) activity, modulating the gene expression of c-Myc, Cyclin D, Axin2, among others [16,17]. On the other hand, Wnt non-canonical pathways involve a great variety of target proteins, depending on the cell type and context. Among them, the best characterized are the Planar Cell Polarity (PCP) [18] and the calcium pathway [19], frequently activated by Wnt4, Wnt5a, and Wnt11. In recent years, various alternative pathways activated by these Wnts have been described but not fully characterized, most of them are linked to the regulation of cell proliferation and adhesion, such as the Wnt/RAP1, Wnt/ROR, Wnt/PKA, Wnt/PKC, and Wnt/mTor pathways [2,20,21].

3. ROR receptors

In 1992, Masiakowski y Caroll described two new cell membrane receptors in a neuroblastoma cell line. Since their cytoplasmic portion had a domain with high homology with the tyrosine kinase domain of growth factor receptors, they were included within the RTK family and called Orphan Tyrosine Kinase Receptors 1 and 2 (ROR1 and ROR2), because their ligands were unknown at that time [22]. Over time, orthologues of ROR2 gene were described in various species such as *Drosophila melanogaster* (dROR) [23], *Caenorhabditis elegans* (cam-1) [24], *Aplysia californica* (Apror) [25], *Danio rerio* (Ror2) [26], *Gallus gallus* (cRor2) [27,28], *Xenopus laevis* (XRor2) [29], and *Mus musculus* (mRor2) [30].

Structurally, the extracellular region of RORs can be divided into 3 large domains: an immunoglobulin (Ig) type, a FZD or cysteine-rich domain (CRD), and a Kringle domain (KNG). On the other hand, the intracellular portion has 4 additional domains: the tyrosine kinase domain (TKD), a serine/threonine rich domain (S/TRD), followed by a Proline-Rich Domain (PRD), and a second S/TRD at the carboxy-terminal end [31] (Fig. 1). In humans, ROR1 and ROR2 have 58% amino acid identity and share all their functional domains. In particular, the CRD, Ig, and TKD domains share the highest homology (78%, 73%, and 66%, respectively). Likewise, among different groups of vertebrates and invertebrates, RORs possess a high level of conservation, particularly in KNG domains, reflecting the physiological importance of these proteins [24,32,33] (Fig. 1).

The tyrosine kinase function of ROR2 has been well established by Yamamoto et al., (2007) and Mikels et al. (2009) [34,35]. However, some studies have proposed that the TKD domain lacks biological function, being categorized as a pseudo-kinase [36]. Nonetheless, there is no doubt this receptor has a critical role in the transduction of signals to various proteins [6].

4. ROR2 expression

During the early stages of organogenesis, ROR2 expression is found in the brain, neural tube, cephalic neural crest cells, and primitive line [37]. As development advances, ROR2 is detected in the ocular epithelium and the

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skeletal (throughout all extremities), cardiac, respiratory, and nervous systems [38,39]. ROR2-/- knockout mice present severe abnormalities in skeletal and heart development. Furthermore, ROR2-/- and ROR1 -/- knockout exhibited an even more severe phenotype, showing that both receptors play a crucial role in development with non-overlapping functions [40].

Analysis of ROR2 expression in human tissues using the GTEx (Genotype-Tissue Expression) database revealed that most adult tissues express low levels of *ROR2* (< 10 TPM, transcripts per million) and a few tissues express *ROR2* at the lower end of the medium expression range (10 – 1000 TPM) (Fig. 2). These results were partially confirmed by Morioka et al. (2009) that evaluated ROR2 expression in 23 normal adult tissues by northern blot. They found that *ROR2* was weakly detected in the thyroid and stomach [41], which correlates with GTEx data, but they observed an absence of expression in the colon, prostate, and ovary, that express medium levels of ROR2 according to GTEx. Several publications have determined the protein expression of ROR2. For example, Lara et al. (2010) reported ROR2 expression in colorectal gland mucosa of healthy colon epithelium [42]. Furthermore, in colon cancer, ROR2 was shown to be expressed on CD19+ B cells, and even more, in the subpopulation of CD19+/CD5+ B cells [43]. Additionally, its expression was described in untransformed adult human osteoblasts and pancreas in adulthood [44,45]. Without any doubt, further studies that clarify the expression of this receptor in healthy adult tissues will be helpful to better understand ROR2 function in adulthood.

5. Wnt/ROR2 signaling

Non-canonical Wnt ligands bind to ROR2 by its CRD domain, which shows great similarity to the domain present in FZD proteins [24]. Wnt5a activates ROR2 by promoting its phosphorylation at S864 via GSK3β [46]. Moreover, ROR2 autophosphorylation and complete activation of its tyrosine kinase domain is achieved once CKIε phosphorylates five tyrosine residues of the PRD [47]. Once fully activated, the signaling pathways triggered downstream of ROR2 vary widely, as do their effects on cellular behavior. One of these pathways is JNK, with subsequent activation of the actin-binding protein, Filamin A, which promotes cell migration and invasion [48,49]. The PKC pathway is also activated by this complex, regulating genes linked to cell invasion and motility [50]. Other pathways activated by ROR2 not necessarily in a Wnt5a-dependent manner will be described in the next section. Apart from Wnt5a, other members of the Wnt family have been reported to interact with ROR2. Morioka et al. showed that Wnt5b interacts with ROR2, which increases cell invasion [41]. Furthermore, Wnt11 was described to interact with ROR2 by its CRD domain, promoting cellular invasion via Rho/ROCK signaling. This study revealed that ROR2 triggers the expression of Wnt11, suggesting an auto-stimulatory loop [51]. The authors also showed that the inhibition of Wnt11 reverts the increase in invasion rate induced by ROR2 overexpression in breast cancer [51], reinforcing the importance of ligand-receptor interaction for ROR2 downstream signaling and function. In line with this, Billiard et al. demonstrated, in osteoblastic cells, that Wnt1 and Wnt3 could bind ROR2, but interestingly, the interaction with Wnt1 potentiates its signaling, while with Wnt3 it inhibits it [44]. However, Wnt1-ROR2 binding did not modulate the kinase activity of this receptor, suggesting that another molecular event is needed to fully activate ROR2 apart from ligand binding, such us dimerization or co-receptor binding.

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Apart from ligand-receptor interaction, some authors described the ROR2 downstream signaling pathways activated as part of the Wnt non-canonical pathways. It has been demonstrated that the multiple pathways activated by Wnt5a/ROR2 are implicated in β-catenin abundance regulation, by promoting or inhibiting its cytoplasmic accumulation and degradation. For example, Kremenevskaja et al. (2005) described that signaling via Wnt5a/ROR2 increases the activity of the Ca^{2+}/CAMKII pathway, promoting the phosphorylation of β-catenin, accelerating its degradation and inhibiting the expression of oncogenes such as c-Myc [52]. Likewise, in colon cells, Wnt5a/ROR2 pathway is shown to increase mRNA and protein levels of E-ubiquitin ligase SIAH2, which will promote the degradation of β-catenin, preventing its entry into the nucleus and subsequent gene expression linked to cell proliferation and motility [53]. Conversely, Wnt5a/ROR2 activates ADP-Ribosylation Factor 6 (ARF6) in gastrointestinal cells which leads to an increase on β-catenin cytoplasmic levels by disrupting β-catenin and N-cadherin interaction. As a result, β-catenin is readily available to translocate to the nucleus and enhance the expression of genes linked to cell invasion [54].

6. ROR2 in cancer

Aberrant expression of ROR1 and ROR2 in adult tissues has been associated with the progression of various pathologies, including numerous types of cancer. Whereas ROR1 overexpression was consistently shown to contribute to the progression of different types of tumors, the studies on ROR2 have showed opposite results in different tumor types. Together with functional data that will be summarized below, these observations suggests that ROR2 has a dual role in tumor development, being able to act either promoting or inhibiting cancer progression in different tumors, a feature also described for other developmental pathways, such as Notch [55]. It is likely that this pleiotropic role of ROR2 in cancer is due to the engagement of various co-receptors and Wnt ligands and the presence of extracellular inhibitors of this non-canonical pathway [3].

Another major difference with ROR1, is that ROR2 expression can be either downregulated or upregulated in cancer compared with normal tissues. A comparison of ROR2 expression in tumor and normal matched tissues using data from The Cancer Genome Atlas (TCGA) revealed higher ROR2 levels in tumor tissue in HNSC and LUSC and lower in KIRP and THCA (Fig. 3). This is in agreement with previous studies showing an increase in ROR2 expression in laryngeal squamous cell carcinoma [56], tongue squamous cell carcinoma [57], and oral squamous cell carcinoma [58]. However, data from other studies do not match with those from the TCGA [59-61], which in some cases might be attributed to the analysis of different tumor subtypes.

In addition, ROR2 expression becomes undetectable in those types of cancer whose progression is dependent on the canonical Wnt pathways (or β-catenin dependent), which correlates with the inhibitory role of ROR2 exerted on canonical Wnt pathways. Alternatively, high levels of ROR2 have been detected in those tumor types considered independent of β-catenin or of the non-canonical pathways, in which it is given a critical role in tumorigenesis [62].

6.1. ROR2 as a tumor promoter

In recent years, ROR2 expression was shown to associate with tumor progression by enhancing several cancer-related features such as proliferation, invasion, migration, anchor-independent growth, epithelial-mesenchymal

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transition (EMT), and *in vivo* tumor growth (Table 1). The downstream signaling events activated by ROR2 are summarized in Figure 4 and discussed in the following sections. These findings reveal that although cancers within this group have different tissues of origin, the cellular processes and downstream pathways activated by ROR2 up-regulation were similar in most of them. In addition, in some of these studies, ROR2 levels correlate with worse clinical outcomes, low overall survival, and metastatic stages. This suggests ROR2 as a useful prognostic marker and a novel therapeutic target.

Interestingly, apart from its role and expression on tumor cells, ROR2 has been detected in the tumor stroma of some types of cancers, contributing to cancer progression. For example, in epithelial ovarian cancer, the serous subtype expresses higher levels of ROR2 in the stroma, suggesting ROR2 as an interesting target to disrupt the interaction between tumor and stroma [63]. Moreover, it was described that ROR1 and ROR2 favors cancer cells dissemination to the omentum, and particularly ROR2 participates in stromal activation during ovarian cancer metastasis [64].

Similar observations were made in pancreatic cancer. In this case, high stromal ROR2 is correlated with regional lymphatic metastasis and TNM stage together with reduced survival [65]. Moreover, another study by Carbone et al demonstrates that adipocytes induce EMT and aggressiveness in pancreatic ductal epithelial cells [66]. Additionally, adipocytes overexpress many soluble modulators of the non-canonical Wnt pathways, such as FRZB, SFRP2, RSPO1, Wnt5a, and Wnt5b. Also, adipocytes induce an increase in ROR2 levels of pancreatic ductal epithelial cells, which suggests that the soluble modulators secreted end up activating ROR2 and inducing its nuclear shuttling in a paracrine way [66]. This is interesting because ROR2 was shown to be overexpressed in adipose mesenchymal stem cells by IL-6/sIL-6R via STAT3 in chronic inflammatory tissues [67]. This relates to the previously mentioned regulation of ROR2 in ovarian cancer by LPS, LTA, or IL-6 also via JAK/STAT3 and NF-κB [68]. These findings reflect the importance of ROR2 expression in stromal cells and how it could influence tumor progression, particularly in a pro-inflammatory tumor microenvironment.

6.1.1. Mechanisms regulating the positive effect of ROR2 on proliferation and cell cycle progression

It was shown that the overexpression of ROR2 in osteosarcoma increased cell proliferation and colony formation *in vitro*, together with an increase in cell viability [41, 72, 73]. Moreover, ROR2 silencing in osteosarcoma cells caused an arrest in G0/G1 phases, which correlates with a reduction in c-Myc, Cyclin D1, Cyclin E, and CDK4 levels [74]. It has been described that in CLL cells ROR2 oligomerizes with ROR1 upon Wnt5a binding, and consequently recruits guanine exchange factors (GEFs), particularly ARHGEF1, ARHGEF2, and ARHGEF6. These GEFs activate Rac1, which promotes cell proliferation [43]. Activation of Rac1 by ROR2 together with Cdc42 activation and increased cell proliferation was also described in malignant pleural mesothelioma [93]. ROR2 was also shown to promote anchorage-independent growth *in vitro* and tumor growth *in vivo* in renal cell carcinoma which was mediated by an increase in MMP2 expression [59]. These observations were supported by Yang et al., who described that ROR2 overexpression is related to an increase in proliferation, together with a decrease in apoptosis. These changes are linked to higher expression of genes involved in the cell cycle, such as PCNA, CDK1, and MMP2 [76]. This role of ROR2 in renal cell carcinoma was also supported by observations by Rasmussen et al. [60]. In breast cancer, ROR2 overexpression promotes cell proliferation by activating MAPK/p38 pathway. Once activated, p38 leads to the overexpression of CDK2,

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CCND2, and Ki67 [86]. In addition, an increase in p-Akt levels was demonstrated in breast cancer tumors overexpressing ROR2. PI3K/Akt activation by ROR2 is shown to increase proliferation and tumor diameter together with a decrease in apoptosis [85].

6.1.2. Mechanisms regulating the positive effect of ROR2 on EMT, migration, and invasion

ROR2 overexpression promotes cell invasion and migration in many tumor types such as osteosarcoma [41, 71, 72], ovarian cancer [76], breast cancer [83], esophageal and oral squamous cell carcinoma [58, 75], renal cell carcinoma [60, 76], melanoma [91], malignant pleural mesothelioma [94], gastrointestinal stromal tumor (GIST), desmoid-type fibromatosis (DTF), and leiomyosarcoma (LMS) [95]. The modulation of these processes by ROR2 seems to be dependent on the upregulation or activation of Rho family GTPases, small molecules that share structural homology and become activated only when bound to GTP. The best-characterized molecules in this family are Rho, which controls the stress fibers and focal adhesion formation, and Rac and Cdc42, which regulate membrane ruffling, and filopodium formation, respectively. These two proteins are described to be activated by ROR2 in malignant pleural mesothelioma which contributes to an invasive phenotype [93]. Likewise, the complex formed by Wnt5a, ROR1, and ROR2 described above in CLL, recruits GEFs to activate RhoA and increase cytokine-directed migration [43]. One of such GEFs, ARHGEF1, was shown to increase invasion and migration in breast cancer through ROCK activation, a major downstream target of RhoA [84]. ROR2 was also shown to mediate invasion of esophageal squamous cell carcinoma by activating RhoA, Rac1, and ROCK [74, 83, 96]. In both osteosarcoma and esophageal squamous cell carcinoma, activation of RhoA occurs via DAAM1 [75, 97].

ROR2 has been also associated with the epithelial-mesenchymal transition (EMT), where it promotes the mesenchymal phenotype, characterized by reduced cell-cell interactions and increased motility and invasiveness. Xu et al. described that ROR2 silencing inhibited ovarian cancer migration, invasion, and induced morphologic alterations compatible with an epithelial phenotype [79]. In addition to the classical EMT morphological changes, ROR2 has been implicated in changes in protein levels of EMT markers. In ovarian cancer ROR2 silencing results in upregulation of epithelial markers E-cadherin and keratin and downregulation of mesenchymal markers N-cadherin and vimentin. Moreover, ROR2 was shown to regulate the expression of EMT key transcription factors such as Snail and Slug [79]. In renal cell carcinoma, ROR2 was shown to regulate the levels of Twist, another key EMT transcription factor [76]. Also, in osteosarcoma, the Wnt5a/ROR2 complex is activated by Snail-induced EMT suggesting a positive feedback loop between Wnt5a/ROR2 and EMT [69]. Through the activation of EMT transcription factors, ROR2 can mediate changes in the transcription of genes required for invasion. For instance, ROR2 activity favors extracellular matrix (ECM) remodeling by upregulating MMP2 in renal cell carcinoma [59, 60] and osteosarcoma [69] leading to an increase in migration and invasion. Similarly, Henry et al. also described a positive effect of ROR2 on migration and invasion [77]. An inhibitory effect on migration was described upon ROR2 silencing, and a more marked effect was observed when co-silencing with ROR1 [64, 78], suggesting a possible interaction between these receptors as described in CLL. ROR2 overexpression has been described to regulate migration and invasion by activating other signaling pathways including the MAPK/JNK [71, 77, 83] and MAPK/p38 pathways [86]. In breast cancer, the activation of MAPK/p38 correlates with an increase in MMP2, MMP9, Snail, N-cadherin, TIMP1, Vimentin, and TGFβ

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expression favoring cell migration and invasion [86]. In multiple myeloma, ROR2 activates S6K and 4E-BP1 via AKT/mTOR and correlates with a decrease in cell adhesion of cancer cells to their microenvironment [88]. In melanoma, Wnt5a/ROR2 complex activates PKC, which phosphorylates ROR2 in a positive feedback loop. This phosphorylation promotes the internalization of ROR2 via clathrin, and posterior motility, invasion and metastasis of melanoma cells [91]. Moreover, the effect of ROR2 overexpression in promoting invasion was particularly described in hypoxic conditions for this cancer, showing the importance of the tumor microenvironment in the phenotypic plasticity of cells [92]. Wnt5a/ROR2 signaling was also described to be modulated by inflammatory mediators in response to NF-κB and STAT3 activation. This regulation enhanced migration in ovarian cancer particularly linked to inflammation [68].

6.1.3. Mechanisms regulating the effect of ROR2 on increased therapeutic resistance

ROR2 overexpression was shown to contribute to tumor progression by increasing the resistance to therapeutic agents. In ovarian cancer, expression of both ROR1 and ROR2 was correlated with an increase in cisplatin-resistance and silencing of both ROR receptors sensitized cells to cisplatin [78]. Furthermore, Veskimäe et al. described that ROR2 upregulation was correlated with the development of platinum resistance in ovarian cancer, together with the upregulation of Wnt5a, STAT3, and NF-κB levels [81]. Likewise, a 10-fold increase in BRAF-inhibitors resistance was observed after ROR2 overexpression in melanoma, particularly in hypoxic conditions [92].

6.1.4. Clinical significance of ROR2 overexpression

ROR2 overexpression has been shown to correlate with the poor prognosis of patients with various tumor types. For instance, increased ROR2 expression correlated with worse overall survival in squamous cell carcinoma [57], GIST and LMS [94], pancreatic ductal adenocarcinoma [65], neuroblastoma [95], renal [59], breast cancer [77] and urothelial carcinoma [96]. Moreover, ROR2 expression was shown to be significantly expressed in metastatic tissues from pancreatic ductal adenocarcinoma [65], melanoma [92], breast [82, 86], non-small cell lung [87], primary and papillary thyroid [61, 89], ovarian [63], cervix cancer [90], and urothelial carcinoma [95]. Furthermore, ROR2 levels correlated with T stage, high histological grade, vascular invasion, and worse disease-free survival in urothelial carcinoma [96].

6.2. ROR2 as a tumor-suppressor

The tumor-suppressing role of ROR2 has been established in different tumor types as described in Table 2. In these cancers, ROR2 has been linked to inhibition of proliferation, migration, invasion, colony formation, cell cycle progression, and tumor growth *in vivo*. In some cases, ROR2 was shown to promote apoptosis and a greater sensitivity to chemotherapies [3, 6].

In some of the cancers listed in Table 2, tumor progression occurs in patients with ROR2 downregulation, demonstrating the relevance of the tumor-suppressing functions of ROR2. This is the case of hepatocellular carcinoma [100], medulloblastoma [104], advanced stages of high-grade serous ovarian carcinoma [105], gastric [101], prostate [103], and colon cancer [98]. In some cases, ROR2 downregulation is mediated by promoter

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methylation [55, 98]. On the contrary, a high expression of ROR2 which correlates with a decrease in tumor progression has been observed in other tumor types (i.e. endometrial cancer and medulloblastoma) [80, 104].

Of note, contradictory findings have been described in some tumor types. For example, in colon cancer, many groups reported a decrease in ROR2 expression by promoter methylation and an association with poor prognosis and survival [42, 69, 98]. However, another report described that higher ROR2 expression in tumor samples was correlated with TNM stage and lymphatic metastasis [106]. The reasons for these discrepancies remain unclear. Similarly, it was shown that low expression of ROR2 was detected in prostate cancer cells and tumor samples, particularly in metastatic samples compared to primary tumors or adjacent normal tissue. This study also correlated lower levels of ROR2 with poor prognosis and overall survival. Moreover, it showed that ROR2 inhibits prostate cancer metastasis by regulating the PIAS3–PI3K–AKT2 signaling axis [103]. However, a previous article showed that ROR2 mediates the effect of Wnt5a on promoting the invasion of prostate cancer cells [107]. Over the years, many groups have described ROR2 over-expression in ovarian cancer and its correlation with tumor stage [63, 68, 77-80, 105]. However, in 2019, Li et al. demonstrated an opposite role for ROR2 in a particular ovarian cancer type, the high-grade serous ovarian carcinoma, where ROR2 over-expression was correlated with better prognosis (Table 2) [105]. In this case, the discrepancy could be explained by the fact that ROR2 functions are cell and context-dependent, and this could differ between different subtypes of ovarian cancer with different molecular backgrounds. Nevertheless, it is possible that the divergences between some studies derive from the use of different ROR2 antibodies, some of which might present non-specific binding as described by Ma and coworkers [108].

The role of ROR2 as a tumor suppressor is mediated by various signaling pathways that are depicted in Figure 5 and discussed in the upcoming sections. Interestingly, some of the pathways shown in Figure 5, were also implicated as mediators of ROR2's role in cancer progression (Figure 4). For example, the tumor-suppressing role of ROR2 is mediated by inhibition of the PI3K/Akt pathway in some cancers such as prostate cancer [103] and other common carcinomas such as nasopharyngeal, esophageal, gastric, colorectal, hepatocellular, lung, and breast carcinoma [55]. This contrasts with the activation of this pathway by ROR2 that promotes cell proliferation and adhesion as mentioned in sections 6.1.1. and 6.1.2. The mechanisms by which ROR2 can alternatively activate or inhibit the PI3K/Akt pathway have not been established but reveal a marked tumor type-dependency on the signaling pathways regulated by ROR2.

6.2.1. Inhibitory mechanisms of ROR2 on proliferation, cell cycle progression, and apoptosis

In colorectal cancer, ROR2 downregulation by promoter methylation decreased JNK and NFAT1 levels, together with an increase in *in vivo* and *in vitro* proliferation, suggesting an anti-proliferative role of ROR2 in this cancer [42, 98]. The effect of ROR2 on JNK was also described in high-grade serous ovarian carcinoma where ROR2 over-expression induced unfold protein response together with an up-regulation of BIP, p-IRE1α, CHOP, p-JNK, and p-c-Jun. This results in an increase in apoptosis and a decrease in tumor growth by activating the IRE1α/JNK/CHOP pathway [105]. Additionally, in gastric cancer, ROR2 overexpression inhibited proliferation and induced apoptosis independently of Wnt5a. This effect on proliferation is related to an arrest on G0/G1 phase, and with a decrease in nuclear β-catenin and c-Myc levels, showing the effect of the non-canonical ROR2 pathway in inhibiting canonical Wnt pathways [101]. Concerning this, *ROR2* expression is

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associated with CTNNB1 (β-Catenin 1) gene mutation, which contributes to non-canonical pathway deregulation in medulloblastoma [104]. Moreover, mesenchymal stem cells (MSC, one type of stromal cell associated with gastric tumors) were reported to express higher levels of Wnt5a and ROR2 than cancer cells, which increases the proliferation of cancer cells when co-cultured. This effect was mediated by Wnt5a-ROR2 signaling by enhancing CXCL16 secretion in MSC, which may act on CXCR6 expressed by cancer cells [109].

Furthermore, in various carcinomas such as nasopharyngeal, esophageal, gastric, colorectal, liver, lung, and breast carcinomas, ROR2 over-expression inhibits Akt and GSK3β, leading to a decrease in Cyclin D1 and c-Myc levels. This results in the inhibition of proliferation together with a cell cycle arrest and increased apoptosis. For this reason, ROR2 is frequently methylated in these carcinomas and this favors tumor progression [55].

6.2.2. Mechanisms regulating the negative effect of ROR2 on EMT, migration, and invasion

In prostate cancer, ROR2 overexpression suppressed miR-199a-5p expression, which increases PIAS3 levels. Therefore, p-Akt and Akt are down-regulated, inhibiting migration, invasion and, EMT proteins [103]. Moreover, in esophageal squamous cell carcinoma, nasopharyngeal carcinoma, and breast adenocarcinoma, the inhibition of Akt in response to ROR2 overexpression, inhibits migration and invasion, together with an increase in E-cadherin levels and a decrease in N-cadherin and fibronectin levels, which is accompanied by a phenotypical change of the cells from epithelioid to a more spindle-like type [55]. Additionally, in colorectal cancer, ROR2 knockdown decreased JNK and NFATC1 levels, together with a decrease in migration of cancer cells [98]. In endometrial cancer, the ROR2 promoter is also methylated in particular tumor subtypes [102]. Moreover, ROR2 overexpression in endometrial cancer cell lines decreased cell invasion [80, 102] and migration [80]. These functional changes were accompanied by an increase in E-cadherin and a decrease in vimentin levels, which correlates with a possible effect on EMT [102].

6.2.3. ROR2 effect on increased chemosensitivity

There is only one article describing a link between ROR2 and increased chemosensitivity. In the esophageal squamous cell carcinoma cell line KYSE150, ROR2 over-expression increased the chemosensitivity to doxorubicin, together with a decrease in cell viability accompanied by an arrest in G2/M phases, increased apoptosis, and inhibition of cell motility [55]. Although it was shown that ROR2 inhibits the PI3K/Akt pathway in this cell line the underlying mechanisms of chemoresistance were not investigated.

6.2.4. Clinical significance of ROR2 expression

Loss of ROR2 expression in cancer is often related to tumor progression. ROR2 is downregulated in metastatic prostate cancer compared to primary tumors and normal tissue, and this correlates with a worse overall and progression-free survival [103]. Similarly, both worst overall and progression-free survival after the loss of ROR2 expression is observed in medulloblastoma patients, together with a positive correlation among Wnt5a, ROR2, and β-catenin expression [104]. ROR2 expression was also found to inversely correlate with tumor stage and Ki67 levels in hepatocellular carcinoma [100]. Loss of ROR2 expression in endometrial cancer is associated

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with an increase in adhesion, migration, and invasion, together with worse overall survival [80]. Particularly in high-grade and serous subtype endometrial cancer, ROR2 is inhibited by the methylation of its promoter [102]. Finally, in high-grade serous ovarian carcinoma, advanced tumor stages and lymphatic metastasis express lower levels of ROR2, suggesting that ROR2 can be a prognostic marker of the early stages of this type of ovarian cancer [105].

7. ROR2 as a therapeutic target

The unprecedented jump achieved during the last decade in understanding the molecular mechanisms of cancer had allowed the development of targeted therapies, an approach that offers the promise of being more selective and less harmful than conventional therapies [110]. Given the role ROR1 and ROR2 receptors play in the progression of various types of cancer, their restricted expression in adult tissues, and their overexpression in tumor cells, they have been considered as potential targets for new therapies [111]. Moreover, their localization in the cell surface had made them excellent targets for monoclonal antibodies (mAb). Accordingly, many mAb targeting ROR1 are in advanced clinical trials for different tumor types, such as CLL, metastatic breast cancer, and B-cell Lymphoid Malignancies [112-114].

Similarly, Hellmann et al. described and validated twelve high affinity fully human anti-ROR2 antibodies, making them good candidates for the therapy of various cancers where ROR2 showed a pro-tumorigenic role [115]. Moreover, a rabbit humanized ROR2 mAb was recently shown to induce cytotoxicity of ROR2-expressing cells following conversion to a T cell-engaging bispecific antibody [115]. Another approach to target this receptor is the use of antibody-drug conjugates (ADC). One of these ADC, BA3021, is being evaluated in phase 1 and 2 clinical trials in patients with advanced solid tumors (NCT03504488). Moreover, Chimeric Antigen Receptor T (CAR-T) cell therapy has been considered as a possible therapeutic strategy. In this line, two CAR-T are being tested in interventional studies: CCT301-38 and CCT301-59 are in phases 1 and 2, respectively, both designed to treat recurrent or refractory stage IV Renal Cell Carcinoma (NCT03393936). Additionally, CCT301-59 is also being tested in other refractory solid tumors, such as soft tissue sarcoma, gastric, pancreatic, and bladder cancer in phase 1 clinical trial (NCT03960060).

8. Conclusions

Unlike ROR1, ROR2 expression and function are highly dependent on the cellular context and tumor type. In some cancers, ROR2 is overexpressed and promotes tumor progression whereas in others the advancement of the tumor is observed when ROR2 is downregulated. Interestingly, ROR2 exerts these dual functions by regulating certain biological processes in opposite ways. For instance, ROR2 increases or decreases cell proliferation by regulating both cell cycle progression and expression of its regulatory proteins in a positive or negative manner, respectively. Similarly, ROR2 was shown to both enhance and inhibit cell migration and invasion. It has been demonstrated that ROR2 promotes cancer progression by stimulating several cancer-related pathways. In contrast, the molecular pathways implicated in the tumor-suppressing functions of ROR2 have been less studied. Similar to the dual effect of ROR2 on several biological processes, ROR2 was shown to either activate or inhibit the PI3K/Akt pathway in different tumor types. The reasons underlying these differences in ROR2 functions still need to be established, however, the identification of signaling pathways and

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biological processes in those tumor types where ROR2 is pro-tumorigenic have positioned ROR2 as a promising protein for targeted therapy.

9. Key unanswered questions

The numerous studies published during the last years have contributed to elucidating the role of ROR2 in various cancers. However, many unanswered questions remain to be investigated. Chief among them is to determine which components of the ROR2 signaling pathway are critical to tilt ROR2 functions toward tumor progression or tumor suppression. This is not an easy task due to the complexity of the Wnt/ROR pathway. Another outstanding question is to determine weather the biological processes activated by ROR2 are dependent or independent of upstream Wnt activation. If the former is true, it would be important to determine which Wnt activates ROR2 in different tumor types. Another critical aspect of ROR2 that has not been studied in depth is how the expression level of ROR1 affects the processes regulated by ROR2. Since ROR1 is likely to compete with ROR2 both for Wnt ligands and intracellular mediators, it is anticipated that ROR2 functions can be profoundly altered by changes in ROR1 levels.

Figure Legends

Figure 1. Structure of ROR receptors in various species. Scheme of ROR2, with its characteristic extracellular (Ig, CRD and KNG Domain) and intracellular (TKD, S/TRD and PRD) domains in different species. hRor1/2: human, mRor1/2: mouse, CAM-1: *C. elegans*, y dRor: *D. melanogaster*.

Figure 2. ROR2 expression in human adult tissues according to GTEx. The bar graph shows ROR2 TPM in several adult tissues. Colors indicates different levels of ROR2 expression: below the cutoff (red, <0.5 TPM), low (blue, 0.5 – 10 TPM) and medium (green, 10 – 1000 TPM).

Figure 3. ROR2 expression in tumor and normal matched tissues. Data from TCGA were plotted using GEPIA. Box-Plot of ROR2 expression in tumor (red) and normal (green) samples. BRCA: Breast invasive carcinoma; HNSC: Head and neck squamous cell carcinoma; KIRC: Kidney renal clear cell carcinoma; KIRP: Kidney renal papillary cell carcinoma; LUAD: Lung adenocarcinoma; LUSC: Lung squamous cell carcinoma; THCA: Thyroid carcinoma;T: tumor tissues; N: normal tissues. Analysis was done for groups with a sample size greater than 30 patients using GEPIA2.

Figure 4. ROR2 signaling pathways implicated in tumor promotion. ROR2 regultates proliferation, migration and invasion by phosphorylating (blue), activating (green) or altering expression (red) of proteins from the AKT, p38, RhoA/ROCK, PCK and JNK pathways. Particularly, DAAM1 activation occurs upon binding of Wnt5a to ROR2.

Figure 5. ROR2 signaling pathways implicated in tumor supression. ROR2 regulates proliferation, apoptosis, migration and invasion by phosphorylating (blue), activating (green) or altering expression (red) or nuclear traslocation (orange) of different proteins of AKT, JNK and UPR (Unfolded Protein Response) pathways, together with EMT related proteins.

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Competing interests

The authors declare that they have no competing interests

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