The Ror-Family Receptors in Development, Tissue Regeneration and Age-Related Disease

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The Ror-family proteins, Ror1 and Ror2, act as receptors or co-receptors for Wnt5a and its related Wnt proteins to activate non-canonical Wnt signaling. Ror1 and/or Ror2-mediated signaling plays essential roles in regulating cell polarity, migration, proliferation and differentiation during developmental morphogenesis, tissue-/organo-genesis and regeneration of adult tissues following injury. Ror1 and Ror2 are expressed abundantly in developing tissues in an overlapping, yet distinct manner, and their expression in adult tissues is restricted to specific cell types such as tissue stem/progenitor cells. Expression levels of Ror1 and/or Ror2 in the adult tissues are increased following injury, thereby promoting regeneration or repair of these injured tissues. On the other hand, disruption of Wnt5a-Ror2 signaling is implicated in senescence of tissue stem/progenitor cells that is related to the impaired regeneration capacity of aged tissues. In fact, Ror1 and Ror2 are implicated in age-related diseases, including tissue fibrosis, atherosclerosis (or arteriosclerosis), neurodegenerative diseases, and cancers. In these diseases, enhanced and/or sustained (chronic) expression of Ror1 and/or Ror2 is observed, and they might contribute to the progression of these diseases through Wnt5a-dependent and -independent manners. In this article, we overview recent advances in our understanding of the roles of Ror1 and Ror2-mediated signaling in the development, tissue regeneration and age-related diseases, and discuss their potential to be therapeutic targets for chronic inflammatory diseases and cancers.

Keywords: non-canonical wnt signaling, cell polarity, migration, proliferation, stem/progenitor cells, cellular senescence, inflammation, cancers

INTRODUCTION

In the developmental process, various cell behaviors, including cell polarization, migration, proliferation, and differentiation, are strictly regulated based on genetic programs, and thereby establishing proper morphogenesis and tissue-/organo-genesis. The regulation of these cell behaviors is also essential for proper tissue repair or regeneration following injury even in the adult tissues. For example, tissue stem/progenitor cells initiate their proliferation and differentiation in response to local environmental changes including inflammation caused by injury (Kizil et al., 2015; Xiao et al., 2020). The signaling mechanisms involved in the regulation of the developmental processes and responses following injury should be activated or inhibited at the appropriate strength and timing. Therefore, their aberrant activation under the pathological conditions such as chronic inflammation with aging might contribute to the progression of various diseases.
The Ror-family proteins, Ror1 and Ror2 act as receptors or coreceptors for non-canonical Wnt ligands such as Wnt5a, thereby regulating cell polarity, migration, proliferation, and differentiation that are required for proper developmental morphogenesis and tissue-organo-genesis (Minami et al., 2010; Endo and Minami, 2018). Ror1 and Ror2 are expressed selectively in some undifferentiated cells including stem/progenitor cells, implying that in addition to the amount of their ligands, the gene regulation of the Ror-family receptors is important for their actions. In this review, we first overview the functions of the Ror-family receptors in regulating developmental processes, and then introduce how expression of Ror1 and/or Ror2 is regulated in certain types of cells, including tissue-resident stem/progenitor cells, in adult tissues during tissue repair or regeneration following injury. We also discuss the possible involvement of aberrant signaling mediated by the Ror-family receptors in the stem/progenitor cell aging and the age-related diseases including chronic inflammatory diseases and cancers.

FUNCTIONAL DOMAINS OF THE ROR-FAMILY PROTEINS IN REGULATING NON-CANONICAL WNT SIGNALING

Extracellular Domains

In vertebrates, the Ror-family receptors consist of two structurally related proteins, Ror1 and Ror2. Both Ror1 and Ror2 (hereinafter, referred to as Ror1/Ror2) are type I transmembrane proteins, and their extracellular regions are composed of an immunoglobulin (Ig)-like domain, followed by a frizzled-like cysteine-rich domain (CRD), and then a kringle domain (KD) (Figure 1). The CRDs of Ror1/Ror2 can interact with Wnt5a (Oishi et al., 2003; Mikels and Nusse, 2006; Weissenböck et al., 2019), one of the most extensively studied non-canonical Wnt proteins. A growing body of evidence shows that Ror1/Ror2 act as receptors or coreceptors for various Wnt proteins, including Wnt5a, Wnt5b, Wnt9a, and Wnt11, to regulate various cellular responses (Oishi et al., 2003; Mikels and Nusse, 2006; Fukuda et al., 2008; Morioka et al., 2009; Paganoni et al., 2010; Sato et al., 2010; Endo et al., 2012; Ho et al., 2012; Bai et al., 2014; Weissenböck et al., 2019; Menck et al., 2021). The KD of Ror1 can interact with that of Ror2 to form Ror1/Ror2 heterooligomers that are required for Wnt5a-induced signaling at least in some cellular contexts (Yu et al., 2016). Although the function of the Ig-like domain in the Ror-family receptors remains elusive, Ror1 mutant mice lacking the Ig-like domain exhibit abnormal development of the kidneys when crossed with Ror2 deficient mice or Wnt5a heterozygous mutant mice (Qi et al., 2016), suggesting that Ror1/Ror2 have redundant functions in regulating Wnt5a-induced signaling.

Cytoplasmic Domains

The cytoplasmic regions of the Ror-family receptors contain a putative conserved tyrosine kinase domain (TKD), followed by a serine/threonine-rich domain (S/TRD1), a proline-rich domain

![Figure 1](https://example.com/figure1.png)

**Figure 1** | Schematic representation of the Ror-family receptors (Ror1/Ror2)-mediated signaling, implicated in the regulation of Wnt5a-induced cell polarity, migration, proliferation, and survival. (A) The Ror-family receptors induce filopodia formation and JNK activation via the interaction with FLNa, leading to the regulation of cell polarity and migration. Wnt5a-Ror signaling can also induce activation of c-Src and Dvl, leading to the activation of JNK, c-Src and GSK3, respectively, phosphorylate the Ror-family receptors on their tyrosine and serine/threonine residues, both of which are required for Wnt5a-induced cell polarity and migration. (B) Wnt5a-Ror signaling can activate PI3K-Akt pathway presumably via CKIr associated with Ror1/Ror2, which in turn promotes cell proliferation and survival. c-Src, activated by Wnt5a-Ror signaling, can also induce activation of Akt, thereby contributing to cell proliferation and survival.
(PRD), and another serine/threonine-rich domain (S/TRD2) (Figure 1). Recent studies demonstrate that the TKDs of Ror1/Ror2 act as pseudokinase domains that are incapable of binding to ATP by itself (Sheetz et al., 2020), although they can mediate Wnt5a-induced signaling and cellular responses (Enomoto et al., 2009; Sheetz et al., 2020). It has been shown that the non-receptor tyrosine kinase c-Src can phosphorylate the tyrosine residues within the activation loops in the TKDs of Ror1/Ror2 (Akbarzadeh et al., 2008; Gentile et al., 2014), and that the substitutions of these tyrosine residues with phenylalanine result in the impairment of their several functions (Mikels et al., 2009; Gentile et al., 2014; Sheetz et al., 2020). However, further studies will be required to determine the roles of the tyrosine phosphorylation within the TKDs of Ror1/Ror2 in regulating various cellular behaviors.

The S/TRD1 of Ror2 is required for recruitment and activation of c-Src following Wnt5a-stimulation (Akbarzadeh et al., 2008; Lai et al., 2012). Accumulating evidence demonstrates that c-Src plays essential roles in regulating Ror1/Ror2-mediated cell migration and proliferation (Enomoto et al., 2009; Gentile et al., 2014; Shojima et al., 2015). Ror2 can also bind to other signaling molecules, including flamin A (FLNa) and casein kinase 1 epsilon (CK1ε), via the PRD (Kani et al., 2004; Nishita et al., 2006). Ror2 mediates filopodia formation and c-Jun N-terminal kinase (JNK) activation via the interaction with FLNa, thereby regulating cell polarity and migration (Nishita et al., 2006; Nomachi et al., 2008) (Figure 1A). Interestingly, c-Src has also been implicated in the activation of Dishevelled (Dvl) and c-Jun N-terminal kinase, downstream of Wnt5a-Ror2 signaling (Yamagata et al., 2012) (Figure 1A). Like Ror2, Ror1 might exhibit the same or similar function in regulating polarized cell migration presumably through filopodia formation (Kaucka et al., 2011). The serine/threonine residues within the C-terminal portion of Ror1/Ror2 can be phosphorylated via glycogen synthase kinase 3 (GSK3) and CK1ε, which might be required for the activation of non-canonical Wnt signaling (Kani et al., 2004; Yamamoto et al., 2007; Grumolato et al., 2010; Konopelski Snavely et al., 2021). Indeed, it has been shown that GSK3-mediated phosphorylation of Serine 864 within the STD2 of Ror2 is required for Wnt5a-induced cell migration (Grumolato et al., 2010) (Figure 1A), and that Wnt5a-Ror signaling can also activate phosphoinositide kinase three (PI3K)-Akt pathway presumably via CK1ε associated with Ror1/Ror2, which in turn promotes cell proliferation and survival (Zhang et al., 2012) (Figure 1B).

THE ROR-FAMILY RECEPTORS IN DEVELOPMENT

Embryonic Morphogenesis

Wnt signaling can largely be classified into canonical (β-catenin-dependent) and non-canonical (β-catenin-independent) pathways. Wnt5a can activate the non-canonical Wnt/planar cell polarity (PCP) pathway, in which Dvl activates the Rho-family of small GTPases, including Rho, Rac, and Cdc42, and their downstream effectors, Rho-associated protein kinase and JNK, leading to reorganization of the actin cytoskeleton, and thereby regulating polarized cell morphology and migration. In vertebrates, Wnt/PCP pathway regulates polarized cell movements during convergent extension (CE), by which tissues undergo narrowing along one axis and concomitant extension along another axis. Indeed, Wnt5a-Ror2 signaling can regulate CE movements during gastrulation and neurulation in Xenopus embryos (Hikasa et al., 2002; Oishi et al., 2003; Schambony and Wedlich, 2007; Martinez et al., 2015). In zebrafish, Wnt11, but not Wnt5a, is expressed highly at gastrula-stage embryos and Wnt11-Ror2 signaling is implicated in regulating CE movements during gastrulation (Bai et al., 2014).

In mammals, Wnt/PCP pathway plays essential roles in regulating collective and directed cell movements involved in various developmental processes, including neural tube closure, neural crest migration, the anterior to posterior axis elongation, inner ear hair cell alignment, and heart morphogenesis (Kibar et al., 2001; Curtin et al., 2003; Montcouquiol et al., 2003; Wang J. et al., 2006; Wang Y. et al., 2006; Ybot-Gonzalez et al., 2007; Muñoz-Soriano et al., 2012). Indeed, Ror2−/− and Wnt5a−/− mouse embryos exhibit dwarfism, short limbs and tail, facial anomalies, and ventricular septal defect (Yamaguchi et al., 1999; DeChiara et al., 2000; Takeuchi et al., 2000; Oishi et al., 2003; Schwabe et al., 2004; He et al., 2008), reminiscent of features observed in patients with Robinow syndrome that is caused by loss-of-function mutations in Ror2 or Wnt5a genes (Atalay et al., 1993; Afzal et al., 2000; van Bokhoven et al., 2000; Person et al., 2010). These mutant mice also exhibit disrupted alignment and orientation of inner ear hair cells (Qian et al., 2007; Yamamoto et al., 2008), and disrupted morphogenesis of the kidney, lung, trachea, esophagus, and midgut (Yamada et al., 2010; Kishimoto et al., 2018). Although the phenotypes of Ror2−/− mouse embryos are somewhat milder than those of Wnt5a−/− mouse embryos, severer morphological phenotypes are observed in Ror1/Ror2 double mutant mice (Nomii et al., 2001; Ho et al., 2012), indicating that pleiotropic, yet redundant functions of Ror1/Ror2 during developmental morphogenesis.

Tissue- and Organo-Genesis

During mouse development, Ror1/Ror2 are expressed in various tissues and organs, including the lung, kidney, tooth, and the skeletal and nervous systems (Oishi et al., 1999; Takeuchi et al., 2000; Al-Shawi et al., 2001; Matsuda et al., 2001), and play crucial roles in their establishment by regulating cell proliferation and differentiation as well as cell polarity and migration (Schwabe et al., 2004; Lin et al., 2011; Maeda et al., 2012; Nishita et al., 2014; Zhang K. et al., 2020; Ma et al., 2021).

Nervous System

In the nervous system of mouse embryos, Ror1/Ror2 are expressed in neural stem/progenitor cells (NPCs) within the neocortices (Oishi et al., 1999; Al-Shawi et al., 2001; Endo et al., 2012). At early embryonic stages, NPCs divide actively to maintain the NPC pool and thereby generating a large number of neurons via intermediate progenitor cells (IPC s), neuron-producing transient amplifying cells. Suppressed expression of
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**Regeneration of Muscle**
Although overall expression levels of the Ror-family receptors in adult tissues are reduced compared to developing tissues, expression of Ror1 can be detected in satellite cells (SCs), one of the skeletal muscle-specific tissue stem cells, within the skeletal muscles of the adult mice (Kamizaki et al., 2017). It is well known that SCs play a crucial role in regulating the regeneration of skeletal muscles after injury (Mauro, 1961; Chargé and Rudnicki, 2004). Although SCs are in quiescent state under physiological conditions, they are activated and initiate their proliferation following skeletal muscle injury, then differentiate and fuse with each other to produce new myofibers, thereby promoting skeletal muscle regeneration (Seale et al., 2000). Importantly, expression level of Ror1 in SCs is further increased upon skeletal muscle injury (Kamizaki et al., 2017). Tumor necrosis factor-α and interleukin-1β (IL-1β), inflammatory cytokines produced from inflammatory cells, including neutrophils and macrophages infiltrated into the injured muscles, can induce the expression of Ror1 in SCs through the activation of NF-κB pathway. Further studies in SCs-specific Ror1 conditional knockout-mice have revealed that increased expression of Ror1 in SCs is required for their proliferation following injury and subsequent regeneration of skeletal muscles (Kamizaki et al., 2017).

**Repair in Nervous System**
The adult mammalian brains have a limited capacity to regenerate spontaneously following injury or diseases. Although NPCs exist in some parts even in the adult mammalian brains, there are no stem/progenitor cells involved in generating new neurons to compensate damaged neurons at least within the injured parenchyma. It has been shown that Ror2 expression is increased in the brains following traumatic injury (Endo et al., 2017). Interestingly, increased expression of Ror2 is observed in reactive astrocytes, surrounding the injured sites, that express Nestin, a marker of NPCs. Astrocytes are the most abundant glial cells in the brain and contribute to brain homeostasis. Under pathological conditions, astrocytes change to a state called reactive astrocytes that exhibit various specific properties, thereby affecting the brain functions. In the injured brains, reactive astrocytes acquire stem cell-like properties and start to proliferate (Götz et al., 2015). It has been reported that proliferative reactive astrocytes exhibit anti-inflammatory and tissue-repair promoting functions (Sofroniew, 2015; Frik et al., 2018; Williamson et al., 2021). In astrocyte-specific Ror2 conditional knockout-mice, number of proliferating reactive astrocytes is decreased (Endo et al., 2017), indicating that induced expression of Ror2 in reactive astrocytes plays an important role in promoting repair of the injured brains.

Cell-cycle entry of quiescent astrocytes is triggered by growth factors, including basic fibroblast growth factor (bFGF), where expression of Ror2 can be induced during the transition from G0/G1 to S-phase (Endo et al., 2017). It has been shown that Ror2 is a target gene of E2F1, and that Ror2 suppresses Foxo3a-mediated

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expression of the cyclin-dependent kinase inhibitors p21 and p27 via the PI3K-Akt pathway, leading to activation of E2F1-mediated transcription, thereby promoting the G1/S-phase transition (Endo et al., 2020). Although Wnt5a is not required for the cell-cycle progression stimulated by bFGF, the possible involvement of other Wnt ligands, including Wnt5b and Wnt11, has to be investigated.

### Stem/Progenitor Cell Aging

It is known that the function of adult tissue stem/progenitor cells attenuates with aging that is causally linked to the age-associated impairment in tissue repair, regeneration, and homeostasis. Therefore, it is expected to develop clinical intervention methods for preventing tissue aging, by targeting tissue stem/progenitor cell aging. Dental pulp stem cells (DPSCs) play an important role in maintaining tooth homeostasis and repairing of postnatal tooth (Zheng et al., 2019). Furthermore, DPSCs exhibit multipotent differentiation capacity, and thus have the potential for use in clinical applications not only for dental diseases, but also for systemic diseases (Yamada et al., 2019). They can be isolated from human dental pulp tissues and expanded in culture, but gradually lose their proliferative ability and multipotent differentiation potential during the expansion because of entering cellular senescence. In cultured human DPSCs, Ror2 is expressed highly at earlier passages, but its expression is decreased in senescent DPSCs (Dong et al., 2021). Consistently, decreased expression of Ror2 is also detected in DPSCs isolated from elderly donors compared to those from young donors. Furthermore, Ror2 can inhibit induction of cellular senescence in cultured DPSCs by inhibiting STK4-Foxo1 pathway in a Wnt5a-independent manner (Dong et al., 2021). Therefore, supplementing expression of Ror2 or inhibiting decreased expression of Ror2 in DPSCs might lead to the maintenance of their stemness, which might be useful for the clinical use of DPSCs.

### TABLE 1 | Factors and drugs regulating expression of the Ror-family receptors in cancer cells.

| Types of Cancers | Regulated Genes | Analyzed Samples (Cell line, Clinical Sample etc.) | Regulatory Factors | References |
|------------------|-----------------|-------------------------------------------------|--------------------|------------|
| **Breast cancer** | Ror1            | MDA-MB 231                                      | Induced by activation of glucocorticoid receptor | Obradović et al. (2019) |
|                  | Ror1            | HCC1954                                         | Induced by YAP1     | Islam et al. (2019) |
|                  | Ror1            | Hs578T, MDA-MB 231                              | Induced by Twist    | Cao et al. (2018) |
|                  | Ror1            | BT549, MDA-MB 231                               | Inhibited by miR30a | Wang et al. (2018) |
|                  | Ror1            | Patient derived xenograft                       | Inhibited by treatment with paclitaxel | Zhang et al. (2019) |
| **Ovarian cancer** | Ror1           | Patient derived primary cell                     | Induced by dexamethasone | Karvonen et al. (2020) |
|                  | Ror1            | JHOS2, Ovaxho, Kuramochi                        | Induced along with cisplatin resistance | Veskimäe et al. (2018) |
|                  | Ror2            | Patient sample A2780                             | Induced by STAT3    | Arabzadeh et al. (2016) |
|                  | Ror1            | SKOV3                                           | Inhibited by miR382 | Tan et al. (2016) |
| **Gastric cancer** | Ror1           | MKN45                                           | Induced by STAT3    | Ikeda et al. (2020) |
|                  | Ror1            | AGS, BGC823                                     | Inhibited by miR27b-3p | Tao et al. (2015) |
| **Leukemia**     | Ror1            | Patient sample                                  | Induced by STAT3    | Li et al. (2010) |
|                  | Ror1            | Patient sample                                  | Inhibited by berberine | Mohammadiou et al. (2021) |
|                  | Ror1            | RCH-ACV                                         | Induced by UHRF1    | Chow et al. (2018) |
| **Lung cancer**  | Ror1            | H1975, SK-LC-5                                  | Induced by NK02-1   | Yamaguchi et al. (2012) |
|                  | Ror1            | H1975, PO9, H441, H1299, H2228, HCC4006         | Decreased by geldanamycin (inhibitor of HSP90) | Khaleedian et al. (2021) |
|                  | Ror1            | Gefitinib resistant PO9, erlotinib resistant HCC827 | Inhibited by miR30a-5p | Yang et al. (2021) |
|                  | Ror1            | HCC827                                          | Induced by STAT3    | Wang et al. (2021) |
| **Pancreatic cancer** | Ror1 | Panc1, Mia PaCa1                                 | Induced by SETD8    | Liu et al. (2021) |
|                  | Ror2            | HPDE, HPDE/KRAS                                  | Induced by conditioned medium obtained from adipocytes | Carbone et al. (2018) |
| **Melanoma**     | Ror1            | UACC1273                                        | Inhibited by hypoxia | O’Connell et al. (2013) |
|                  | Ror2            | UACC1273                                        | Inhibited by hypoxia | O’Connell et al. (2013) |
| **Head and neck squamous cell carcinoma** | Ror2    | UPCi: SCC152, SNL899, TU177                      | Induced by E6/E7    | Avincsal et al. (2021) |
|                  | Ror2            | UPCi: SCC152, SNL899, TU177                      | Inhibited by miR338-3p | Yang et al. (2022) |
| **Renal cancer** | Ror2            | 786-0                                           | Induced by HIF1a and HIF2a | Wright and Rathmell, (2010) |
how Ror2 can regulate cellular senescence of these stem/progenitor cells in a cell-type specific manner.

THE ROR-FAMILY RECEPTORS IN AGE-RELATED DISEASES

Inflammatory Diseases
Recently, it has become evident that chronic inflammation is a pervasive feature of aged tissues, and is also the common cause of various age-related diseases, including fibrosis, arteriosclerosis, and neurodegenerative diseases. Therefore, it’s a provocative issue to uncover the molecular mechanisms underlying the development or progression of the age-related diseases due to chronic inflammation, aiming to develop novel clinical intervention methods to prevent or ameliorate the pathologies of these age-related diseases. In this regard, enhanced and/or sustained activation of Ror1/Ror2-mediated signaling induced by prolonged inflammation might be associated with progression of these age-related diseases. In the kidney, expression levels of Ror1, Ror2, and Wnt5a are increased in the progressive fibrotic tissues with persistent inflammation after injury (Li et al., 2013). In the damaged kidneys from Ror2−/− mice, reduced disruption of the tubular basement membrane (TBM) along with reduced expression of MMP-2 in tubular epithelial cells were observed compared to Ror2+/+ mice (Li et al., 2013), suggesting that Wnt5a-Ror2 signaling might play an important role in disrupting TBM via MMP-2 during renal fibrosis. Furthermore, Wnt5a and Ror2 are expressed highly in foam cells within the atherosclerotic plaque (Akers et al., 2018; Zhang C.-J. et al., 2020). Aberrant expression of Wnt5a in vascular smooth muscle cells (VSMCs) reduces expression of adenosine triphosphate-binding cassette A1, a key cholesterol transporter, via Ror2, resulting in the enhancement of cholesterol accumulation and inflammatory response in VSMCs (Zhang C.-J. et al., 2020), suggesting that Wnt5a-Ror2 signaling plays a critical role in the pathogenesis of atherosclerosis. A critical role of Wnt5a-Ror2 signaling has also been reported in the dextran sulfate-induced colitis mouse model, where sustained up-regulation of Wnt5a can be observed in stromal fibroblasts in the ulcerative lesions of these mice, and Wnt5a-Ror2 signaling activated in dendritic cells can promote interferon-γ signaling, thereby promoting colitis (Sato et al., 2015). Ror2 expression is also increased in degenerating neurons by IL-1β secreted from activated microglia in the spinal cord of mice with experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis (Shimizu et al., 2016). Wnt5a- or Wnt11-Ror2 signaling can mediate IL-1β-induced neuronal cell death, suggesting that Ror2-mediated signaling might promote the pathology of the neurodegenerative diseases.

Cancer Progression
Since most of cancers are developed in elderly people than young people, it is conceivable that aging and cancer development are tightly related. Accumulating evidence demonstrates that age-related chronic inflammation plays important roles in the progression of cancers (Coussens and Werb, 2002; Ostan et al., 2015). Interestingly, Ror1/Ror2 are expressed highly in various types of cancers (Zheng et al., 2016; Bayerlová et al., 2017; Hossein et al., 2017; Hasan et al., 2018; Astudillo, 2021). Enhanced expression of Ror1 and/or Ror2 in cancer cells can promote their proliferation, migration, invasion, survival or chemoresistance through activation of Rho-family GTPases, c-Src, MAP kinases or Akt in Wnt5a-dependent and/or -independent manners (Enomoto et al., 2009; Zhang et al., 2012; Ida et al., 2016; Nishita et al., 2017; Hasan et al., 2019). In addition, several studies have indicated that Ror1 might be ideal therapeutic target of cancers including leukemia and breast cancer (Karvonen et al., 2017; Choi et al., 2018; Wallstabe et al., 2019; Zhang et al., 2019; Stüber et al., 2020). These studies surmise that increased expression of Ror1 and/or Ror2 in cancer cells is important for their progression. Here, we describe the mechanism how expression of Ror1/Ror2 is upregulated in cancer cells by taking aging into account (see below).
Accumulating evidence has shown that expression of the Ror-family receptors in cancer cells can be regulated by multiple factors and drugs (Table 1). In breast cancers, increased expression of Ror1 can be attributable to reduced expression of miR30a, a suppressor of Ror1 (Wang et al., 2018), which is up-regulated by aging, and age-related up-regulation of miR30a induces cellular senescence (Muther et al., 2017). miR30a can inhibit expression of Ror1 to suppress the progression of breast cancer, however, its expression level is reduced in breast cancer cells, resulting in up-regulation of Ror1 and promotion of the progression of breast cancer.

Furthermore, up-regulated expression of Ror1 can be mediated by STAT3 in various types of cancer cells, thereby promoting proliferation of cancer cells in Wnt5a-dependent or -independent manners (Li et al., 2010; Ikeda et al., 2020; Wang et al., 2021). STAT3 has been shown to be activated in several aged tissues with chronic inflammation (Chazaud and Mouchiroud, 2014; O’Brown et al., 2015), and thus might contribute to the age-related progression of cancers through expression of Ror1. In the case of gastric cancers, constitutive Wnt5a-Ror2 signaling in bone marrow-derived mesenchymal stem cells (MSCs) induces expression of CXCL16, and that CXCL16 secreted from MSCs promotes proliferation and migration of undifferentiated gastric cancer cell line MKN45 cells through inducing expression of Ror1 via STAT3 activation (Takiguchi et al., 2016; Ikeda et al., 2020). Considering that senescent MSCs secrete cytokines and chemokines (Lunyak et al., 2017), it can be assumed that aging might be one of critical factors promoting progression of cancers.

CONCLUSION AND PERSPECTIVES

The Ror-family receptors play important roles in establishing developmental morphogenesis and tissue-organo-genesis in redundant, yet pleiotropic manners. The activation of the Ror1/Ror2-signaling might be regulated by the induction of their expression by themselves, in addition to the stimulation with their ligands, including Wnt5a. Although expression levels of Ror1/Ror2 are kept lower in most of adult tissues than developing ones, expression of Ror1 and/or Ror2 are increased transiently in specific cells, including stem/progenitor cells, following injury or inflammation, via environmental cues including inflammatory cytokines, contributing to the promotion of tissue repair or regeneration (Figure 2A). Furthermore, the Ror-family receptors seem to play a role in maintaining the stemness of tissue stem/progenitor cells, and thereby preventing the induction of their cellular senescence. Therefore, it can be assumed that decreased expression of the Ror-family receptors in the tissue stem/progenitor cells might lead to the dysfunction of these tissue stem/progenitor cells.

On the other hand, expression of Ror1 and/or Ror2 might be induced in various types of cells under chronic inflammation associated with aging, thereby contributing to the development or progression of the age-related diseases, including neurodegenerative diseases and cancers (Figure 2B). Therefore, it will be interesting to clarify the molecular mechanisms how expression of Ror1/Ror2 can be regulated in association with aging or cellular senescence.

AUTHOR CONTRIBUTIONS

ME, KK and YM wrote the manuscript, ME made the figures, KK made the table.

FUNDING

This work was supported by grants from Japan Agency for Medical Research, Development (AMED) [JP21gm1210005(YM) and JP21gm5010001(YM)], JST (Moonshot R and D) [JPMJMS 2022 (YM)] and KAKENHI from Japan Society for the Promotion Science (JSPS) [21K15504 (KK)]. This work also received funding from the collaborative research project program (PRISM) (ME) supported by Sumitomo Dainippon Pharma Co., Ltd. The funder was not involved in the writing of this article and the decision to submit it for publication. All authors declare no other competing interests.

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Conflict of Interest: This work received funding from the collaborative research project program (PRISM) (M.E.) supported by Sumitomo Dainippon Pharma Co., Ltd.

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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