The CD70-CD27 axis in oncology: the new kids on the block

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Abstract
The immune checkpoint molecule CD70 and its receptor CD27 are aberrantly expressed in many hematological and solid malignancies. Dysregulation of the CD70-CD27 axis within the tumor and its microenvironment is associated with tumor progression and immunosuppression. This is in contrast to physiological conditions, where tightly controlled expression of CD70 and CD27 plays a role in co-stimulation in immune responses. In hematological malignancies, cancer cells co-express CD70 and CD27 promoting stemness, proliferation and survival of malignancy. In solid tumors, only expression of CD70 is present on the tumor cells which can facilitate immune evasion through CD27 expression in the tumor microenvironment. The discovery of these tumor promoting and immunosuppressive effects of the CD70-CD27 axis has unfolded a novel target in the field of oncology, CD70.

In this review, we thoroughly discuss current insights into expression patterns and the role of the CD70-CD27 axis in hematological and solid malignancies, its effect on the tumor microenvironment and (pre)clinical therapeutic strategies.

Keywords: CD70, CD27, Hematopoiesis, Oncology, Hematological malignancies, Solid tumors, Combination therapies

Background
In the last decade, the emergence of immunotherapy has revolutionized the treatment of hematological and solid cancers by relying on cancer destruction through activation of the host’s immune system [1, 2]. In solid tumors, immune checkpoint inhibitors, such as anti-CTLA-4, anti-PD-1 and anti-PDL1 have demonstrated the therapeutic potential of immunotherapy, resulting in Food and Drug Administration (FDA)/European Medicines Agency (EMA) approvals, and have become the standard of care in over 50 types of cancer as single agents or in combination strategies [3]. While clinical effectiveness of immune checkpoint inhibition is quite limited in hematological tumors (except Hodgkin lymphoma), chimeric antigen-receptor (CAR) T cells are reshaping the field of hematological malignancies and have led to FDA/EMA approvals since 2017, especially against the B cell antigen CD19 [4]. However, the sobering reality is that generally speaking only a minority of patients benefit from long-term remission [5, 6].

New immunotherapeutic targets could lead to more effective treatment alternatives as single agents or in rationally designed combination strategies. In this regard, the CD70-CD27 axis, belonging to the tumor necrosis factor (TNF) superfamily, has become an attractive target to exploit in oncology [7]. In physiology, the receptor, CD27, is generally found on naive T and memory B and T cell populations and subsets of natural killer (NK) cells. On the other hand, CD70 is only transiently expressed on antigen-activated B and T cells, NK cells and mature
dendritic cells. Upon activation of CD27 by CD70, the extracellular domain of CD27 is cleaved off and found as a soluble fragment (called sCD27) in body fluids [8]. In oncology, CD70 is aberrantly expressed on malignant cells without (solid tumors) or with CD27 co-expression (hematological malignancies), facilitating immune evasion through the tumor microenvironment (TME) and tumor progression [7, 8]. In addition, high levels of sCD27 have been found in serum samples of patients with hematological and solid malignancies, suggesting the involvement of the CD70-CD27 axis [9–14]. This review discusses the role of the CD70-CD27 axis during normal hematopoiesis, the biological effect of its dysregulation in hematological and solid malignancies and the promising role of CD70 as target in the clinic.

The CD70-CD27 axis in hematopoiesis

In hematopoiesis, the hematopoietic stem cells (HSCs) balance self-renewal capacity with multilineage potential. In this way, durable cell levels can be maintained while giving rise to progenitor, precursor and eventually fully differentiated blood cells of the myeloid and lymphoid lineage [15]. A role of the CD70-CD27 axis in the early development stages could only be demonstrated in mice. Multiple studies observed CD70 expression on murine HSCs and progenitor/precursor cells [16–19]. Moreover, Nolte et al. [20] showed that the interaction of CD27 positive (CD27⁺) progenitor cells with CD70 inhibited leukocyte differentiation [20]. Therefore, it has been suggested that the CD70-CD27 axis mediates a negative feedback system, enabling the activated immune system to modulate hematopoiesis [20]. With regard to human hematopoiesis, there is no hard evidence of CD27 and/or CD70 expression on human HSCs and progenitor cells [12, 21], suggesting that the early development stages are independent of the CD70-CD27 axis. By way of contrast, expression of both CD70 and CD27 is found on their malignant counterparts (further discussed in the next section).

Knowledge on expression patterns of CD70 and/or CD27 on more differentiated cells indicate a role for the CD70-CD27 axis during downstream hematopoiesis, however the underlying mechanisms are not yet uncovered. Some studies report the expression of CD27 after commitment to the lymphoid lineage on human B cell progenitor/precursor populations [22–24]. While research on circulating immature and naive B cells showed no CD27 expression, CD70 was found to be transiently upregulated on activated B cells upon antigen encounter. Interestingly, studies investigating B cell differentiation found that CD70-CD27 interactions are important in formation of memory and plasma B cells. Accordingly, within the germinal centers of secondary lymphoid tissue, expression of CD27 is moderate on B cells, upregulated on plasma cells and maintained on a large subset of memory B cells [25–28]. On the other hand, CD70 expression has only been reported on a small subset of germinal center B cells [27, 29].

In human thymocyte development, CD27 expression could only be detected on the latest stage [30, 31]. Moreover, a few studies showed that human thymic stromal cells that provide essential signals for T cell development and clonal selection express low levels of CD70 [29, 32]. The function of the CD70-CD27 axis in human thymic development still needs to be uncovered. In mice it is shown that this interaction is not essential for the generation of conventional CD4⁺ and CD8⁺ αβ T cell populations [33], while it is important in the functional differentiation of the low abundant γδ T cell subsets [34]. Opposite to naïve B cells, multiple studies reported CD27 expression on almost all naïve T cells and subsequent activation resulted in CD70 upregulation which diminished again after gaining full effector functions [35, 36]. As seen for B cells, CD27 expression is present on regulatory T cells (Tregs) [37] and on memory T cells [33, 38].

Besides B and T cells, CD70 and CD27 expression is also found to be strictly regulated on human NK cells. Here, it could be demonstrated that CD27 is upregulated during the latest stage of development and is downregulated on the majority after gaining effector functions. Similarly to previous results on B and T cells, CD70 is only transiently upregulated upon NK cell activation [39, 40].

Although more research is necessary to unravel the molecular mechanisms during early cell development, CD70 and CD27 on mature immune cells operate as costimulatory molecules and their interaction contributes to immune regulation via different signaling pathways. It is seen that CD27 signaling activates the NF-κB and c-Jun kinase pathways via bound T RAF2/5, leading to cell proliferation, survival and differentiation. Additionally, triggering of CD27 can result in apoptosis as well via the receptor-associated death domain-containing adaptor protein Siva [8]. Finally, it was shown by different studies that CD70 can exert reverse signaling through induction of PI3K/Akt and MEK signaling pathways regulating cell expansion, differentiation and effector functions [41–44].

Altogether these data show that the CD70-CD27 axis is tightly regulated during hematopoietic cell development showing either CD70 or CD27 expression but generally never co-expression of both markers. In addition, interaction of these costimulatory molecules orchestrates important signaling pathways on mature B/T cells and NK cells shaping immune responses. Given the biological functions of the CD70-CD27 axis, it is not surprising
that acquisition or overactivation of the axis by abnormal expression patterns can contribute to malignancy. In the next paragraph, the aberrant expression patterns and associated signaling that has been found for a considerable number of hematologic and solid tumors will be discussed. An overview of expression patterns and signaling in physiology and oncology is depicted in Fig. 1.

The CD70-CD27 axis in oncology

Expression on hematologic malignancies

Leukemia  Leukemic stem cells (LSCs) can be seen as the malignant counterparts of HSCs as they account for initiation and maintenance of the disease, and share self-renewal capacity and multipotency to give rise to more differentiated malignant cells [15]. Although absent from normal HSCs, constitutive expression of CD27 is detected on LSCs of acute myeloid leukemia (AML) and chronic myeloid leukemia (CML) patients [12, 21, 45]. In addition, CD70 is co-expressed on LSCs from AML patients [12]. Co-expression of CD70 and CD27 is also present on AML [12] and B cell acute lymphoblastic leukemia (B-ALL) blasts [10, 22, 46, 47], on malignant B cells of chronic lymphocytic leukemia (B-CLL) and subtypes including hairy cell leukemia and its prolymphocytic variant [10, 48–51]. Finally, high levels of sCD27 were detected in serum samples from AML patients and were associated with inferior prognosis [12].

Fig. 1  The CD70-CD27 axis in hematopoiesis and oncology. During normal hematopoietic development, expression of CD70 is tightly regulated and plays a role in priming, survival and differentiation for a subset of immune cells through NF-κB and c-Jun pathway activation via TRAF 2/5 leading. Alternatively, apoptosis can be induced by activating the caspase pathway via Siva. Reverse CD70 signaling can activate PI3K/Akt and MEK signaling pathways leading to regulation of cell expansion, differentiation and effector functions. In oncology CD70 and CD27 are frequently co-expressed on malignant cells which can deliver proliferation signals and a growth advantage to the malignant cells. Apart from improved growth, dysregulation of the axis can provide other tumor promoting effects via different signaling pathways. Figure created with BioRender.com. Abbreviations; CSC, cancer stem cell; HSC, hematopoietic stem cell; MEK, mitogen-activated protein kinase kinase; NFκB, nuclear factor kappa B; NK cell, natural killer cell; PI3K, phosphoinositide 3-kinase; sCD27, soluble CD27, TRAF 2/5, TNF receptor associated factor 2/5
B cell lymphoma and multiple myeloma  The presence and relevance of LSCs in CML and AML is generally accepted, but whether other hematologic malignancies arise from similar populations is still unclear [52]. Nonetheless, CD27 is identified on a rare B cell population that may be responsible for the generation and maintenance of the characteristic Reed-Sternberg cells of Hodgkin lymphoma and on a population suggested to be multiple myeloma stem cells [53–55].

Co-expression of CD70 and CD27 can be found on the surface of malignant B cells in non-Hodgkin lymphomas (NHL) such as diffuse large B cell lymphoma (DLBCL) [7, 51, 56], follicular lymphoma [56, 57], follicle center lymphoma [51], mantle cell lymphoma [7, 50, 51, 58, 59], Burkitt lymphoma [51], and Waldenström macroglobulinemia [60]. Of interest, high levels of CD70 were related to an unfavorable outcome with a shorter overall survival in different types of DLBCL [61]. In addition, as seen for AML, sCD27 has been identified as a prognostic factor for different NHL subtypes [11, 14]. In Hodgkin lymphoma, a different expression pattern was observed whereby Reed-Sternberg cells show high CD70 levels but lack the expression of CD27 [54, 62, 63].

Expression of CD70 and CD27 is also detected on malignant plasma cells in multiple myeloma, where CD27 decreases with increasing progression of the disease and its absence might even be a prognostic factor for high-risk disease [64, 65]. The related plasma cell leukemia by way of contrast shows robust CD27 expression [66].

T cell lymphoma  Constitutive CD27 and CD70 expression has also been detected on T cell neoplasia such as anaplastic large cell lymphoma [7, 67], peripheral T cell lymphoma [7], cutaneous T cell lymphoma [68–72], adult T cell leukemia/lymphoma [73–75] and extranodal NK/T cell lymphoma [7, 76, 77]. On the contrary, only CD70 expression is observed on chronic active Epstein-Barr virus associated T cell lymphoma (a rare complication of latent Epstein-Barr virus infection) [78] and T cell acute lymphoblastic leukemia [79].

In leukemia, it is seen that the CD27 signaling on AML and CML LSCs leads to induction of the Wnt pathway, an important pathway for self-renewal [12, 21, 45]. Schürch et al. [21] revealed that the aberrant activation of the Wnt pathway occurs through ß-catenin activation, a central component of the pathway in the cytoplasm [21]. This impaired Wnt activation resulted in increased proliferation of LSCs [12, 21] and drug resistance [45], both promoting leukemic progression.

Furthermore, the study of Riether et al. [12] observed that CD70/CD27 signaling on immature AML blasts induced stem cell gene signatures through the canonical Wnt pathway (as discussed above), JAK/STAT pathway, Hedgehog pathway and transforming growth factor beta (TGF-ß) signaling. Functional analysis showed that the CD70/CD27 interaction was also responsible for symmetric cell divisions, promoting the immature blast state and preventing myeloid differentiation [12]. The involvement of the CD70-CD27 axis in blastoid formation was also seen in a rare case of low-grade B cell lymphoma, where upregulation of CD70 and CD27 coincided with a highly increased gene expression of galactin 1 and TGF-ß receptor III, suggesting this could be implicated in the MEK and TGF-ß signaling pathway, respectively [80]. Related to this case, CD70 was higher expressed on the blastoid variant of mantle cell lymphoma, a clinically more aggressive form defined by a higher mitotic rate compared to the common mantle cell lymphoma [59].

Additionally, there is increasing evidence that the CD70-CD27 signaling promotes tumor cell proliferation. In leukemia, blocking of the CD70-CD27 interaction in CML [21], AML [12], B-ALL [22] and some cases of B-CLL [51] reduced proliferation of the malignant cells. This effect on proliferation was also seen in B cell lymphoma where CD27 crosslinking increased proliferation of cell lines through augmented protein kinase C activation [81]. Apart from CD27 signaling, CD70 reverse signaling was also reported to increase proliferation in a low-grade B cell lymphoma. Here, CD70 was hinted to have a responsive state (signaling) during remission phases and a non-responsive state during attack [80]. Interestingly, binding of sCD27 to CD70 was shown to induce proliferation on extranodal NK/T cell lymphomas [76].

Finally, the CD70-CD27 axis can affect malignant cell survival. As discussed above, ligation of CD70 with CD27 on CML LSCs mediated drug resistance by compensatory Wnt pathway activation [45]. This increased survival was also observed in plasma cell leukemia where triggering of CD27 with CD70 rescued plasma cells from drug-induced apoptosis via regulation of p38 and ERK 1/2 MAP kinases of the MEK pathway and the downstream transcription

Signaling in hematologic malignancies  The strict expression patterns of CD70 and CD27 during normal physiology allow for regulation of immune responses via immune cell proliferation, differentiation, survival and death depending on the situation and timing. Hematological malignancies show aberrant expression of both molecules leading to dysregulated signaling of the axis, thereby providing the malignant cells with tumor-promoting capacities.
factor AP-1 [66]. In addition, modulation of both anti- and pro-apoptotic proteins, including the Bcl-2 family, has been described to be dependent of the presence of CD70/CD27 on malignant lymphoma cells. However, the exact role of CD70/CD27 in the regulation of survival needs further elucidation [59, 65, 80].

Hence, these different studies report the CD70-CD27 signaling axis as a driver of malignancy in hematologic malignancies supporting stemness, proliferation and survival. An overview of the signaling pathways involved in both hematologic and solid cancers is depicted in Fig. 2.

Expression on solid tumors
Over the past decades, the importance of CD70 on solid tumors has become clear whereby aberrant expression of CD70 on tumor cells has been reported on numerous types of solid tumors with varying expression levels [8]. As such, CD70 expression has been reported on both primary and metastatic tumor resections in renal cell carcinoma, nasopharyngeal carcinoma, glioblastoma, melanoma, lung carcinoma, cervix carcinoma, breast carcinoma, ovarian carcinoma and mesothelioma and was associated with decreased survival [9, 82–86]. Interestingly, CD70 expression was found to be even higher in metastatic specimens of lung carcinoma, pancreatic

![Fig. 2: Signaling pathways of the CD70-CD27 axis in hematologic and solid cancers. In hematological malignancies, CD70-CD27 signaling activates the canonical Wnt, JAK/STAT, Hedgehog and TGF-β pathways which can induce stemness/immature state. In addition, crosslinking of CD27 in a protein kinase C or β-catenin-dependent manner and reverse signaling of CD70 were shown to induce proliferation of the malignant cells. CD70-CD27 signaling can promote survival by regulating kinases of the MEK pathway and transcription factor AP-1 and by the Wnt pathway through activation of β-catenin. In solid tumors, CD70 signaling is associated with cancer stem cells and EMT transition via the induction of EMT-related gene expression (SOX2, CD44, Vimentin, Snail, Slug and β-catenin) and via MAPK activation and RhoE overexpression. Furthermore, hypoxia is identified as a regulator of CD70 expression and is an important factor to promote stemness, migration and invasion of the tumor. Figure created with BioRender.com. Abbreviations: AP-1, activator protein 1; β-cat, β-catenin; EMT, epithelial to mesenchymal transition; JAK/STAT, Janus kinase-signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; PKC, protein kinase C; RhoE, ras homologous E; sCD27, soluble CD27; SOX2, sex determining region Y-box2; TGF-β, transforming growth factor beta; Vim, Vimentin]
carcinoma and osteosarcoma, suggesting the importance of CD70 in progression of the disease [7]. Consequently, therapies targeting CD70 hold great potential to combat both early and advanced stages of cancer. On the contrary, CD70 seems (almost) absent on the tumor cells in Kaposi sarcoma, prostate carcinoma, Langerhans cell histiocytosis and colorectal carcinoma [8, 87]. Although CD70 is prevalent in numerous cancers, CD70 expression patterns may vary among these different tumor types in spatial distribution, intensity of expression and percentage of positive cells.

In contrast to hematological malignancies, expression of CD27 on the tumor cells has never been reported in solid tumors. Nonetheless, CD70-CD27 signaling can occur through the presence of CD27 in the TME facilitating immune evasion and tumor progression by distinct mechanisms [88–91].

**Signaling in solid tumors**

The role of CD70 reverse signaling in tumor progression has already been described in hematological malignancies but is rather undefined in solid tumors. It was reported in melanoma that CD70 expression regulates invasion and metastasis intrinsically, rather than through the TME. Here the study of Pich et al. [91] showed that signaling of CD70 was dependent on its oligomerization. While the monomeric form of CD70 limited the metastatic and migratory ability of melanoma cells, the trimeric form of CD70 enhanced cell migration and invasiveness [91].

Apart from hematological tumors, cancer stem cells (CSCs) have also been identified in solid tumor types where they are recognized as important players in metastasis, recurrence, heterogeneity and drug resistance [92]. Although for many cancers the presence of CSCs is currently under debate, its existence in glioblastoma, breast cancer and colon cancer is now generally accepted [93]. The involvement of CD70 in the generation and/or maintenance of a CSC phenotype has been described in breast cancer, glioblastoma, melanoma, pancreatic carcinoma and non-small cell lung cancer (NSCLC) and thus could serve as a potential marker of stem cells [12, 94]. In breast cancer, these CD70 expressing CSCs displayed a mesenchymal phenotype, self-renewal potential and enhanced metastasis to the lung compared to the CD70− CSCs population that exhibited an epithelial phenotype [94]. CD70 has also been associated with tumor epithelial to mesenchymal transition (EMT), a process by which epithelial cells gain migratory and invasive characteristics in glioblastoma, melanoma, pancreatic carcinoma and NSCLC [91, 95, 96]. Upon silencing of CD70 in glioblastoma cell lines, expression levels of EMT-associated genes, SOX2 and CD44, decreased, resulting in inhibition of tumor growth and migration [95]. In addition, it was shown that β-catenin was significantly reduced after siRNA-mediated knock-down of CD70 expression in human pancreatic cell lines, as well as other EMT-related genes, such as Vimentin, Snail and Slug [97]. In melanoma, CD70 expression led to MAPK activation and RhoE overexpression, thereby promoting tumor migration [91].

Hypoxia is an important factor of EMT, stem-cell maintenance, invasion, metastasis, angiogenesis and resistance to therapy in solid tumors [98]. In renal cell carcinoma, CD70 induction was reported under hypoxic conditions [99, 100]. In support of this notion, a strong constitutive CD70 expression has been described within hypoxic regions of a murine model for NSCLC [101]. Furthermore, it has been reported that hypoxia can increase the number of small protein-carrying packets called vesicles, which regulate inter-cellular communication, leading to changes in the biological activity. Interestingly, a recent study has shown that in the context of lung cancer, hypoxic conditions stimulated the synthesis of tumor vesicle proteins such as CD70, thereby possibly supporting immune suppression [98].

Altogether, these findings underline an important role of CD70 signaling in acquiring aggressive traits in solid tumor types (an overview is shown in Fig. 2).

**The CD70-CD27 axis and the tumor microenvironment**

Along with a pivotal role of the CD70-CD27 axis on malignant cells, dysregulation of these costimulatory molecules can also cooperate to escape anti-tumor immune surveillance in hematological and solid tumor types by distinct mechanisms in the TME.

In glioma and renal cell carcinoma, the CD70-CD27 axis has shown to mediate apoptosis of lymphocytes [89, 102, 103]. Siva is thought to induce apoptosis of T cells by initiating caspase activation after binding of CD70 to CD27 [104, 105]. Next to apoptosis mediated through CD27 signaling, TGF-β is also known to induce apoptosis in a variety of cell types [90]. The study of Yang et al. [90] showed that treatment with TGF-β induced apoptosis of exhausted CD70 positive (CD70+) T cells at a significantly higher rate than CD70− T cells in NHL by acquiring more pro-apoptotic markers, such as caspase-3 [90].

T cell exhaustion is another mechanism by which CD70-CD27 signaling can reduce immune surveillance. In renal cell carcinoma, tumor infiltrating lymphocytes were found to have an exhausted phenotype, which was driven by CD70 expression [106]. Furthermore, TGF-β induced upregulation of CD70 expression via Smad3 and IL-2/STAT5 signaling, resulting in exhaustion of effector memory T cells in B cell NHL. Both TGF-β-induced, as well as pre-existing intratumoral CD70+ T cells, were
found to be functionally exhausted with lower proliferation, signaling transduction, cytokine production and higher expression levels of PD-1 and TIM-3 after treatment with TGF-β compared to CD70− T cells [90]. Whether the interaction between CD70 and CD27 plays a role in TGF-β-induced T cell exhaustion is still not clear. Yet, Yang et al. [90] found TGF-β-mediated down-regulation of CD27 on CD70+ T cells due to shedding of CD27. This loss of CD27 on the cell surface was reversed after blocking of CD70 and led to restored cell function and viability, indicating a potential role of the CD70/CD27 interaction in TGF-β-mediated T cell exhaustion [90].

Thirdly, the CD70-CD27 pathway can mediate immune escape through its effects on Tregs. CD27 signaling resulted in a direct decrease of Treg apoptosis in murine solid tumor models and an indirect increase of Tregs in vitro, mediated via increased secretion of IL-2 by non-Treg CD4+ T cells [88]. Our study showed increased FoxP3 expression and higher CD4+/CD8+ ratios in CD27+ tumor infiltrating lymphocytes surrounding CD70+ tumor cells in NSCLC patients. As such, CD70+ NSCLC cells could exhibit immune suppression through binding of CD27+ Tregs in the TME [9]. In addition to increased numbers, CD70-CD27 interaction also mediated enhanced survival of Tregs of CLL patients due to a decrease of pro-apoptotic Noxa and increase in anti-apoptotic Bcl-2, which resulted in a decreased sensitivity to drug-induced apoptosis [107]. In addition, the study of Yang et al. [108] reported an effect of CD70-CD27 on intratumoral Tregs. The authors found that expression of FoxP3 on intratumoral Tregs was (partially) induced by CD70+ lymphoma B cells and that these cells reduced the proliferation of infiltrating CD8+ T cells, revealing a role for CD70 expressing malignant cells in the development of intratumoral Tregs and immune suppression [108].

A recent study demonstrated that CD27 expression on human Tregs was closely correlated with suppression of CD4+ and CD8+ T cell proliferation, although the underlying mechanisms are still unclear [37]. Even though CD27 signaling has been shown to increase cell survival of both effector T cells and Tregs, their contribution has been shown to depend on the context and the predominance of each of these two cell types [109]. While in a pro-inflammatory environment, such as secondary lymph nodes, survival of effector T cells was enhanced upon CD27 signaling, increased survival of intratumoral Tregs was observed upon CD27 signaling in the context of a chronically inflamed and well-established tumor [109].

The CD70-CD27 interaction may also favor immune escape through the depletion of NK cells. The study of De Colvenaer et al. [110] used a CD70 transgenic mouse model in which all B cells constitutively express CD70 in order to study continuous triggering of CD27 on NK cells. Here, the authors showed that CD27 stimulation by CD70 resulted in reduced CD27 expression on NK cells as well as depletion of predominantly mature NK cells in vivo, which was partially due to increased apoptosis [110].

Another mechanism by which CD70 expressing tumor cells can exert immune suppression is by regulating immunosuppressive myeloid cells, such as macrophages. A recent study reported an association between CD70 expression and infiltration of CD163+ (a marker of M2 macrophages) tumor-associated macrophages (TAMs) in glioblastoma, suggesting a (in)direct role for CD70 in recruitment and/or activation of tumor promoting TAMs [84, 95, 111]. Here, they also showed that the presence of CD70 on tumor cells and CD163 on TAMs correlated with poor prognosis for glioblastoma patients [95].

Even when expression of CD70 is limited on tumor cells, it can find its way to sustain a tumor enhancing environment by hijacking other important players within the TME that contribute to the proliferative and invasive behavior of cancer, such as the cancer-associated fibroblasts (CAFs). These CAFs, present within the tumor margins and/or tumor mass, exist of a heterogeneous population that forms one of the most dominant components in the TME. In particular cancer types, such as colorectal carcinoma and pancreatic cell carcinoma, these CAFs contribute to oncogenesis and therapy resistance [112, 113]. We recently discovered a subset of CD70 expressing CAFs in specimens of colorectal carcinoma patients [114]. These CD70high CAFs were shown to mediate immune suppression in vitro through increased numbers of CD4+ FoxP3+ CD25+ Tregs and IL-2 levels as opposed to the CD70low CAF population, likely mitigated through CD27. In addition, while colorectal carcinoma cells alone showed no migratory ability, the co-culture with CD70high CAFs exhibited a strong increase in migration. In line with the former, the study of Inoue et al. [115] observed an inferior prognosis in colorectal carcinoma patients with CD70high CAFs [115]. The presence of CD70+ CAFs was also described in head and neck squamous cell carcinoma and since a role of CD70 on CAFs is still a very recent finding, it is very likely that other tumor types will follow [116].

These findings underline the role of the CD70-CD27 axis in facilitating immune evasion through different cells of the TME. An overview of the CD70-CD27 axis in the TME in solid cancers is depicted in Fig. 3.

**Regulation of CD70 expression**

So far, the exact underlying mechanisms of CD70+ tumor cells remains largely unknown, although several studies...
suggest that epigenetic alterations regulate CD70 expression. DNA demethylation of the Tnfsf7 promoter gene has previously been suggested to upregulate CD70 on T cells in the context of autoimmune diseases [117]. Along these lines, in the context of cancer, hypermethylation of the promoter region downregulated Tnfsf7 gene expression in an in vitro breast cancer MCF10 model [118]. The promoter site of the CD70 gene contains binding sites for transcription factors, such as AP-1, Sp1, NF-κB and AP-2. While Sp1 has been linked to CD70 upregulation, the other transcription factors might be implicated as well [45]. Apart from epigenetics, other factors have been reported to drive CD70 expression in response to changes in the TME, such as production of TGF-β and proinflammatory cytokines TNF-α and IFN-γ [49], stimulation of the CD40L-CD40 axis [47, 119, 120] and higher expression of hypoxia-related transcription factors HIF-α/β under hypoxia [90, 99, 100, 121]. Induction of CD70 expression has also been linked to cancer types caused by viral infections, such as Epstein-Barr virus and Human T-lymphotropic virus type 1 [73, 74, 78, 122, 123]. Finally, neutralization of endogenous IL-18 was reported to upregulate CD70 in stomach cancer [124].

Targeting CD70

New insights into the tumor progressive role of CD70 further strengthen the rationale of exploiting CD70 in cancer patients, having the potential to (1) specifically eliminate the CD70 expressing cancer cell populations and (2) abrogate the tumor promoting mechanisms by
the CD70-CD27 signaling axis, both in early stage and advanced disease. Since CD70 expression is absent during homeostasis, as opposed to CD27, it has great potential to exploit as a cancer-specific target. It should be noted that activated T/B cells can transiently express CD70 and thus, caution should be taken when evaluating anti-CD70 approaches given that off-target effects remain a challenge.

As such, numerous promising therapeutic approaches targeting CD70 have been under investigation, both in preclinical and clinical settings with the aim of improving treatment outcomes of cancer patients. An overview of all strategies completed or currently undergoing clinical evaluation is shown in Fig. 4 (extensively reviewed in [125]).

**Antibodies**

Antibody-drug conjugates (ADCs) are monoclonal antibodies (mAbs) coupled to a cytotoxic agent, which enable specific binding of the target protein and internalization of the cytotoxic agent resulting in tumor cell killing. Several ADC compounds targeting CD70 have been developed and are undergoing clinical evaluation in hematological and solid cancers [56, 126–129]. Four different ADCs entered the clinic and all have completed phase I, of which development of two compounds, AMG 172 (Amgen) and MDX-1203 (Bristol-Myers Squibb), has stopped [127]. While both ADC compounds of Seattle Genetics (SGN-75 and SGN-CD70A) discontinued clinical testing due to toxicity reasons, the company’s non-fucosylated monoclonal antibody SEA-CD70 is currently undergoing clinical evaluation in a phase I study in patients with myeloid malignancies (NCT04227847). Although ADCs targeting CD70 are a promising approach to mediate selective killing of the tumor cells, these agents rely on the extent of internalization, which can differ greatly among tumor types [130, 131].

Another form of antibody-mediated therapy is based on antibody-dependent cellular cytotoxicity (ADCC) relying on activating effector cells that carry the Fc receptor CD16 (FcyRIII) combined with blocking of the target protein. The most typical Fc-bearing receptor effector cells that are activated upon binding are the macrophages, although other effector cells, such as NK cells, γδ T cells and dendritic cells also mediate ADCC [132]. Cusatuzumab (ARGX-110) has next to complement-dependent cytotoxicity, enhanced ADCC properties due to increased binding to FcγRIIIa (as a consequence of

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**Fig. 4** Overview of ongoing and completed clinical trials with CD70-targeting agents. Completed trials (solid line) and ongoing trials (dashed line) were sorted based on study start date. Antibody-drug conjugates (ADC, blue); Antibody (Ab, Red); Chimeric antigen receptor (CAR, Green). Efficacy data are depicted when available. Abbreviations: ADC, antibody drug conjugate; Ab, antibody; CAR, chimeric antigen receptor; CR, complete remission; PR, partial remission; SD, stable disease; CRi, CR with incomplete hematological recovery; NHL, non-Hodgkin lymphoma; CTCL, cutaneous T cell lymphoma; RCC, renal cell carcinoma; NPC, nasopharynx carcinoma; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; BCL, B cell lymphoma; MM, multiple myeloma; TCL, T cell lymphoma; Pt, patients; Exp, expected
afucosylation) [72, 133, 134]. Its safety profile has demonstrated to be favorable with no dose limiting toxicities in patients with advanced solid and hematological malignancies [133]. In AML, cusatuzumab efficiently eliminated LSCs in patients treated with hypomethylating agents whereas blocking the CD70-CD27 pathway induced differentiation in AML blasts and stem/progenitor cells [135]. One of the challenges that antibodies relying on ADCC are facing, is the inadequate activation and function of the immune effector cells, such as NK cells, since a great number of cancer patients have an impaired immune system [136].

**CAR-therapy**

Chimeric Antigen Receptor (CAR)-T cell therapy harnesses the patient’s own T cells to better recognize and eliminate the patient’s cancer cells by modifying these T cells to recognize tumor antigens in an HLA independent manner. CAR-T cell therapy has already achieved tremendous success in the treatment of hematological malignancies resulting in FDA/EMA approvals for CD19-targeting CAR-T cell compounds: Kymriah (DLBCL, ALL), Yescarta (DLBCL, follicular lymphoma), Breynzani (DLBCL, follicular lymphoma), Tecartus (CML) and Abeccma (MM) [137]. In addition to different CAR-therapies in preclinical development, currently, five anti-CD70 CAR-T based approaches, i.e., anti-hCD70 CAR (NCT02830724), 4SCAR70 (NCT03125577), CAR CD70 (NCT04662294), CTX130 (NCT04438083) and ALLO316 (NCT04696731), are being evaluated in phase I/II clinical trials in patients with hematological and solid malignancies, awaiting results regarding the safety profile and efficacy in these different cancer types. Despite its success in hematological malignancies, it remains challenging to treat solid tumors with this treatment modality due to multiple obstacles, such as trafficking of the transferred cells to the tumor site, penetration into the tumor and maintaining viability [138].

**Combination regimens evaluated in clinical setting**

Combination regimens with CD70 targeting agents have already been explored in clinical setting for certain cancer types. Preclinical research showed that azacitidine, a hypomethylating agent (HMA), upregulated CD70 on AML LSCs, making these malignant cells more susceptible to CD70 targeting [135]. Based on these preclinical findings, a phase I/II study was initiated, combining custuzumab with azacitidine, in previously untreated older patients with AML or high risk myelodysplastic (NCT03030612). Initial results from the phase I/II dose escalation demonstrate hematological responses in all patients with a complete remission in 67% (8/12) and complete remission with incomplete blood count recovery in 17% (2/12) of patients [139]. Additionally, no dose-limiting toxicities were reported and the maximum tolerated dose of cusatuzumab was not reached. These promising results have led to a randomized phase II trial in newly diagnosed patients with AML, unfit for intensive chemotherapy, combining azacitidine with 10 mg/kg or 20 mg/kg of cusatuzumab (NCT04023526) [140].

Another promising regimen that recently entered the clinic is a combination of cusatuzumab and venetoclax (+/− azacitidine) (NCT04150887) [141]. BCL-2 plays an important role in the survival and persistence of AML blasts by sequestering pro-apoptotic BCL-XL. Venetoclax is a selective inhibitor of BCL-2 which results in the release of BAX leading to mitochondrial outer membrane permeabilization and thus apoptosis of LSCs. Although venetoclax demonstrates promising activity in elderly or chemotherapy-ineligible AML patients, successfully eliminating all LSCs remains a major challenge in the effective treatment of AML [142]. Similar to venetoclax, anti-CD70 therapy targets AML LSCs, though by a different mechanism i.e., inhibition of LSC proliferation, stimulation of their differentiation into myeloid cells and effector function-mediated cell killing [135]. Hence, combining two complementary agents that both target AML LSCs could create additive/synergistic antitumor effects and thus minimize drug resistance. Preclinical data could already demonstrate such synergism between cusatuzumab and venetoclax (+/− HMA) on LSCs [143]. Finally, a combination of cusatuzumab with radiotherapy and/or chemotherapy was evaluated in a phase I study in patients with nasopharyngeal carcinoma (NCT02759250). Patients that received prior radiotherapy and/or chemotherapy had longer progression-free survival compared to the cohort of patients that received monotherapy, although it should be noted that the size was too limited for any conclusive statements [144]. Currently there are no new clinical trials evaluating combinatorial approaches of anti-CD70 therapy with either chemotherapy or radiotherapy in solid cancers.

The combination therapy of CAR targeting CD19 and CD70 has already entered the clinic in patients who have relapsed/refractory B cell malignancies after chemotherapy (NCT03125577, NCT04429438). While the clinical study is currently still ongoing, preliminary results from a patient with refractory and relapsed primary central nervous system lymphoma demonstrated long-term disease free survival without inducing severe cytokine release syndrome and CART cell-related encephalopathy syndrome [145].

**Combination regimens evaluated in pre-clinical setting**

Next to the combinatorial regimens with CD70-targeting therapy that have entered the clinic, other innovative
regimens are being explored in a preclinical setting. One of these studies explored the combination of anti-CD70 therapy and a tyrosine kinase inhibitor directed against BCR-ABL1 in CML. Here, BCR-ABL1 kinase is constitutively active in the majority of CML patients and tyrosine kinase inhibitors, targeting the oncogenic product BCR-ABL, are an effective treatment strategy in CML patients [146]. However, similar to AML, disease-initiating LSCs form a major challenge in the treatment of CML due to persistence of drug-resistant LSCs. The tyrosine kinase inhibitor, imatinib, was found to mediate gene expression changes of SP1 (upregulation) and DNMT1 (downregulation) resulting in demethylation of the CD70 promoter in CML cells and thus upregulated CD70 expression and compensatory Wnt signaling in CML cells [45]. In this study, the authors showed that dual targeting of BCR-ABL1 and CD70, synergistically eradicated CML LSCs due to more effective prevention of the Wnt pathway activation and rendering CML LSCs more susceptible to cell killing with anti-CD70 immunotherapy [45]. Thus, dual targeting of BCR-ABL1 and CD70 eliminates LSCs and may overcome therapy resistance.

Different studies report an interesting regimen of CD70-targeting therapy combined with chemotherapy. In NSCLC, it was shown that treatment with cisplatin increased CD70 expression, both on mRNA and protein level. Interestingly, the combination of cisplatin and the anti-CD70 agent cusatuzumab led to synergistic killing of NSCLC cell lines in vitro [101]. In ovarian carcinoma, CD70 expression on tumor cells was associated with clinical resistance to cisplatin [85]. Here, authors showed that CD70 targeting antibodies could inhibit proliferation of chemo-resistant tumor cells. As such, combining chemo and treatment with anti-CD70 antibodies could be used to overcome resistance to chemotherapy. Finally, it was demonstrated that radiotherapy, similar to what was seen with chemotherapy, could increase membrane CD70 expression in glioma, leukemia and lymphoma [35, 147, 148]. As such, combination strategies of anti-CD70 antibodies and chemotherapy/radiotherapy could render malignant cells more susceptible to CD70 targeted therapy.

The different side of the coin
In this review on the CD70-CD27 axis, we focus on immunotherapeutic strategies aiming at eradicating the tumor cells by specifically targeting tumor-associated CD70 overexpression, thereby abrogating the immune suppressive effects driven by chronic stimulation of the CD70-CD27 axis. However, it is noteworthy to mention that other therapeutic strategies are under investigation with the focus on stimulating the CD27 signaling pathway to enhance CTL responses, including the agonistic IgG1 anti-CD27 antibody, CDX-1127/varilimumab and TriMix, a monococyte-derived DC vaccine is activated through electropropagation with mRNA encoding CD40L, CD70 and active TLR4 [149, 150]. The identification of biomarkers and stratification concepts are important to select the appropriate therapeutic strategy of either inhibiting CD70 and/or CD27 activity, based on the underlying dominant functions, that ensures the best fit for the patient. Thus, targeting strategies of both sides of the CD70-CD27 axis may be exploited depending on the cancer type and its TME.

Conclusions
Combinatorial approaches with anti-CD70 targeting therapies have proven their potential in both preclinical and clinical settings. Until now, mono- and combinatorial therapies have mainly been explored in AML, yet other tumor types might benefit from this approach as well. Research in the field has led to more insights into the underlying molecular mechanisms of the tumor promoting and immune evasive role of the CD70-CD27 axis in oncology. Therefore, in addition to existing approaches focused on targeting CD70, strategies that inhibit the signaling pathways involved in the CD70-CD27 axis might become promising novel therapeutic alternatives in the future. Further preclinical research and clinical evaluation of CD70 targeting strategies will provide new insights into the mechanisms and effects of CD70 and might pave the way towards novel treatment options in the field of oncology.
MDS: Myelodysplastic syndrome; DLBCL: Diffuse large B cell lymphoma; HMA: Hypomethylating agent.

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