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Review

Cancer Research

Dependence Receptors and Cancer: Addiction to Trophic Ligands

Benjamin Gibert and Patrick Mehlen

Abstract

Data accumulating over the last 20 years support the notion that some transmembrane receptors are activated not only by their respective ligands but also, differentially, by the withdrawal or absence of these same ligands. In this latter setting, these receptors actively trigger apoptosis. They have been dubbed dependence receptors because their expression confers a state of ligand dependence for survival on the expressing cells. Twenty of these receptors have been identified to date, and several have been shown to inhibit tumor progression by inducing apoptosis. As a corollary, these receptors, or their transduced death signals, are frequently silenced in cancer cells as a selective mechanism to prevent cell death, allowing invasion and metastasis. Drugs aimed at inducing programmed cell death in neoplastic cells by re-engaging the proapoptotic activity induced by unliganded dependence receptors are in late-stage preclinical tests, poised for clinical evaluation. This approach may offer novel opportunities for patient treatments. In this review, we discuss the implications of dependence receptors in limiting cancer progression and address the therapeutic perspectives brought to light by this paradigm. *Cancer Res; 75(24); 5171–5. ©2015 AACR.*

Introduction

It has been known for over half a century that cells depend on stimulation for their survival. Stimulation is mediated by various receptors and sensors. For example, cells may require specific soluble trophic factors, cytokines, hormones, extracellular matrix interactions, cell–cell interactions, or electrical activity for survival. For any given required stimulus, withdrawal leads to programmed cell death. It has generally been assumed that cell death induced by withdrawal of supporting factors is due to the loss of the associated positive survival signals, such as Akt phosphorylation. Although such survival signals are clearly very important, data obtained over the past 20 years argue for a complementary and novel form of signal transduction that actively induces cell death following stimulus withdrawal. This "negative signal transduction" is mediated by specific "dependence receptors" (DR) that induce apoptosis in the absence of the required stimulus (e.g., when unbound by a trophic ligand; Fig. 1), but block cell death in the presence of the required stimulus (e.g., when bound by a trophic ligand). Thus, the expression of a DR creates a state of dependence (or addiction) on its respective ligand. It is fair to say that this notion presenting transmembrane receptors in an "on_A" and "on_B" mode rather than an "on" and "off" mode has received relatively little attention. However, to date, 20 such receptors have been identified (1, 2–6): The nerve growth factor receptor $p75^{NTR}$, RET (rearranged during transfection), the neurotrophins receptors TrkA and TrkC, Kremen-1, EPHA4, MET, ALK, the netrin-1 receptors DCC (deleted in colorectal carcinoma) and UNC5H1-4 (Unc-5 homologue 1–4), neogenin, Plexin D1, the insulin receptor and its related receptor IGF1r, some integrins, and the Sonic Hedgehog receptors Patched (Ptc) and CDON.

How these receptors trigger apoptosis in the absence of their respective ligands is still not completely understood. Because these receptors do not generally share much homology between them, mechanisms of apoptosis induction may also vary. However, most of these receptors have been shown to trigger apoptosis upon a first proteolytic cleavage of their intracellular domains, probably by a locally activated caspase. Mutation in the caspase cleavage site of each DR is sufficient to block receptor-induced apoptosis completely. Along this line, DCC, the prototypical netrin-1 DR, is cleaved with a P1 residue of Asp1290, and the mutation D1290N completely prevents apoptosis induced by DCC (7). The overall working model is that the caspase cleavage of each DR allows the recruitment, by the intracellular domain, of proteins that in turn will trigger apoptosis. How these receptors can engage apoptosis has been reviewed recently (8). Thus, we focus this review on one of the more important questions in the field: What is the role of the proapoptotic function (i.e., the on_B side) of these receptors that have often previously been shown to mediate other disparate biologic processes (via their on_A side). The data obtained so far converge toward a major role of these proapoptotic receptors in the control of tumor progression.

Dependence Receptors as Constraints for Tumor Progression

Because these receptors trigger apoptosis in the absence of ligand, it has been hypothesized that a tumor can grow independently of ligand limitation only by selecting a mechanism that silences DR-induced cell death. This was formally shown in the case of the prototypical DR DCC. By generating a mouse model in which the netrin-1 receptor DCC was point mutated at the caspase cleavage site, it was shown that inactivation of the proapoptotic

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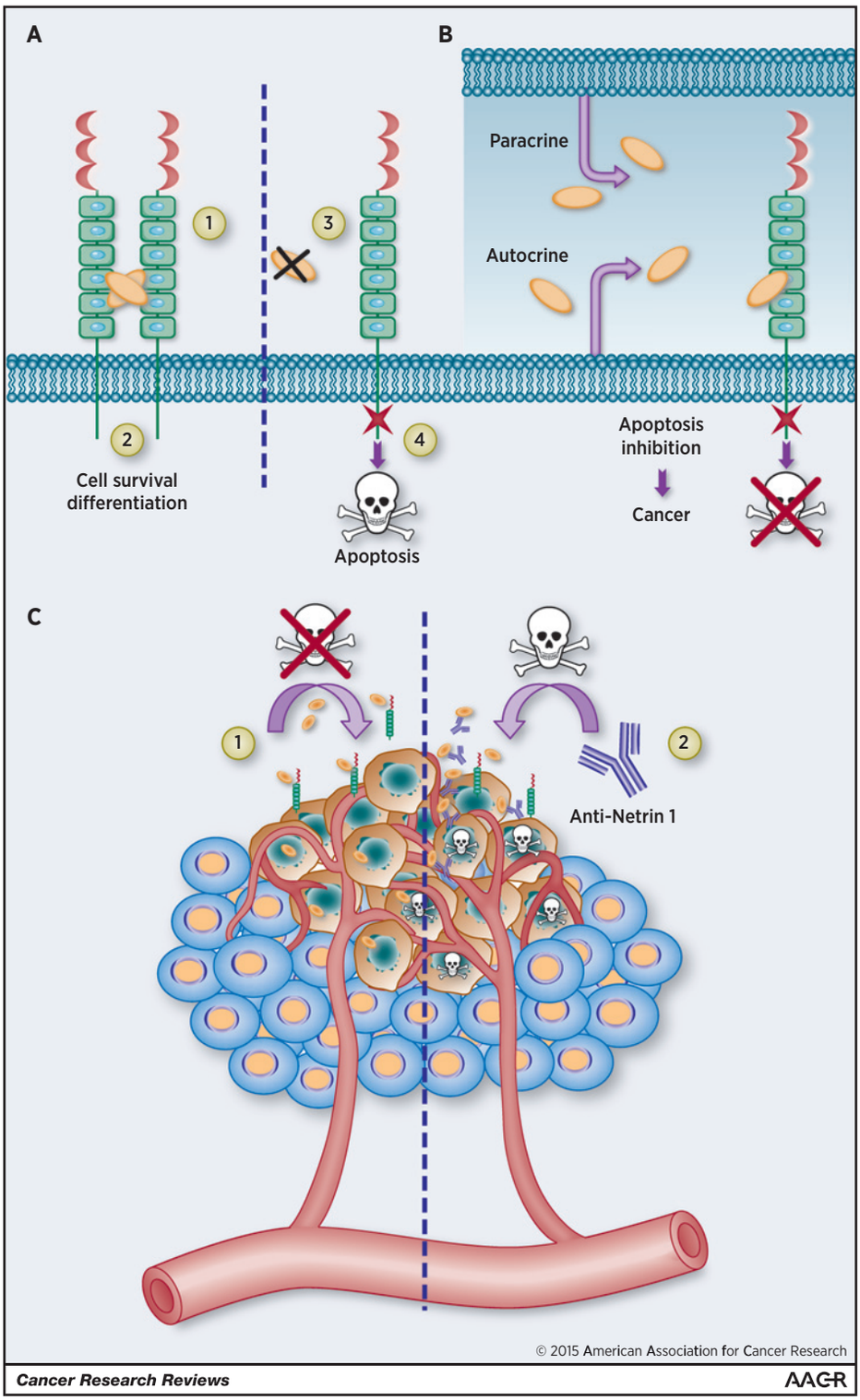

Figure 1.
A, in the physiologic situation, DRs such as DCC share the property of inducing two types of signaling according to the presence or the absence of their respective ligands. 1 and 2, in the presence of ligand, DRs dimerize or multimerize and transduce a positive signal known to promote cell survival, migration, and/or proliferation. 3 and 4, in the absence of ligand, DRs are monomeric and initiate an apoptotic cell death, in most cases associated with proteolytic cleavage of the intracellular domain of the receptor by caspases. B, in tumor cells, an autocrine or paracrine production of ligand could impair DR-induced cell death (1–2); loss of function (through loss of heterozygosity or epigenetic silencing) of the receptor and loss of proapoptotic partners could also prevent the apoptotic pathway. C, schematic view of DR-induced cell death as therapeutic target in cancer. Monoclonal antibodies (here anti–netrin-1) are able to block ligand–receptor interaction and reactivate cell death in tumors. The figure was obtained and modified from Servier Medical Art.

activity of this receptor is sufficient to promote the development and the aggressiveness of tumors in the intestines (9). Similar data were obtained by the Berns's group using mice conditionally deleted for DCC (10). These data echo the initial description of DCC as a colon tumor suppressor, whose expression is lost in the large majority of colorectal cancers, as discovered by Fearon and Vogelstein (11). According to the DR paradigm, a tumor, to grow independently of DR ligand presence, must silence DR-induced

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cell death, and the simplest way to achieve this would be to inactivate the receptor. Interestingly, not only DCC, but also more recently other DRs such as UNC5H, TrkC, and CDON, have been shown to be negatively regulated in various cancer types (6, 12, 13); moreover, the inactivation of DCC, UNC5H, or CDON in mice is associated with tumor progression (6, 10, 12). The decreased expression of DRs in various tumor types occurs either through loss-of-heterozygosity (LOH), transcriptional or epigenetic regulation (12–16). CDON expression has recently been shown to be decreased in neuroblastoma and correlated with patient prognosis. Interestingly, the microRNAs such as the miR-181 family, and in particular the mir181-a and b isoforms, are overexpressed in aggressive forms of neuroblastoma and appear to silence CDON expression by transcript destabilization or translation inhibition (17).

One major question with respect to designating DRs as tumor suppressors has been the question of mutation in cancers. DCC, initially reported as only rarely mutated, has finally been shown to be the third most frequent mutated gene in sun-exposed melanoma (18). UNC5H receptors have been shown to be mutated in sporadic colorectal cancer (14). More generally, the recent efforts in whole-genome sequencing in cancer have revealed that DRs are frequently mutated in various cancers. It is too early to tell whether such reported mutations are driver mutations and whether, as expected according to the mode of action of these DRs, they are loss-of-proapoptotic signaling mutations. As an initial example, the case of TrkC is very interesting. As a tyrosine kinase receptor, the reported mutations in TrkC have been classically considered as oncogenic-gain-of-kinase activity. However, recent studies have shown that at least some mutations detected in different cancers are not gain-of-kinase activity mutations but rather loss-of-proapoptotic activity mutations (13, 16). Along the same line, we reported a loss-of-proapoptotic function mutation in UNC5C in familial cases of colorectal cancer. This mutation was shown to confer an increased risk of developing colorectal cancer (19). Even though a second study showed only a trend toward increased risk (20), it calls for a larger analysis of the importance of DR mutations in cancer, and also supports the view that loss-of-proapoptotic activity mutations in DRs may actively participate in tumor progression.

Inactivating mutations of Ptch, as well as loss of expression, are found in different cancer types such as basal cell carcinomas (BCC), rhabdomyosarcomas, and medulloblastomas. However, to date these mutations have been assumed to activate the Hedgehog–Smo–Gli canonical pathway. One possibility is that Ptch inactivation has a dual effect, both by activating the pro-oncogenic Hedgehog canonical pathway and by silencing the death-inducing DR pathway. In support of this possibility, enforced expression of Ptch in cancer cells lacking Ptch is associated with cancer cell death that is independent of the Hedgehog canonical pathway (21–23).

One puzzling issue is why some DRs have been shown to be upregulated in various cancers rather than being silenced, in apparent contradiction to the DR paradigm. In most cases, the upregulated DRs are tyrosine kinase DRs. For example, the Met receptor is upregulated in many cancers (24). The current and accepted general view of this gain of expression is that it confers pro-oncogenic advantage—for example, increased migratory capacity—through increased kinase-dependent signaling. However, if indeed these receptors act as DRs, one would expect to see an increased sensitivity to cell death. Nonetheless, this cell death may be masked by the prosurvival signals associated with the upregulation of these receptors, and it may explain why kinase inhibitors are associated not only with antiproliferative effects but also with cell death effects (25, 26). Another explanation for the absence of silencing of some DRs in different cancer types is that the programmed cell death DR pathway is turned off by another mechanism. As an example, DAPK, a powerful effector of the death induced by UNC5H or neogenin, is silenced in many cancer types (27–29).

A Novel Therapeutic Approach?

Because DRs induce cell death in territories where the ligand is limited, another selective advantage for a tumor, in addition to inactivating mutations in the DRs, is to avoid the DR Damocles sword by producing the appropriate DR ligand. This may have two advantages for the tumor: The ligand may stimulate the positive signaling of these DRs that is often associated with promigratory, pro-proliferative effect—that is, DCC and most other DRs, as well, have been shown to activate ERK/MAPK upon ligand binding (30, 31). The second, and potentially more important, advantage is that it blocks DR-mediated cell death induction. As several DRs share the same ligand—for example, netrin-1 binds to DCC and UNC5A,B,C,D DRs, SHH binds to Ptc and CDON DRs—upregulation of one ligand could block the death induced by several DRs. Along this line, netrin-1 was found to be overexpressed in a large variety of tumor types such as breast, lung, ovarian cancer, neuroblastoma, and medulloblastoma (32, 33). Netrin-1 was also more specifically shown to be associated with metastasis (34, 35). The pro-oncogenic effect of netrin-1 expression was demonstrated *per se* by using mice overexpressing netrin-1 in the gut. These mice were more prone to develop intestinal cancer (36). Similarly, several *in vitro* and animal proof-of-concept studies have shown that interference of netrin-1–receptor interaction—for example, by silencing netrin-1 or by using a recombinant netrin-1 trap—is associated with netrin-1–expressing cancer cell death and *in vivo* tumor growth and metastasis inhibition. Interestingly, in tumor cell lines and tumor specimens where netrin-1 is expressed at a low level, treatment with conventional drugs—that is, doxorubicin, 5-fluorouracil, paclitaxel (Taxol), and cisplatin—is often associated with an upregulation of both netrin-1 and its receptors, probably because netrin-1 and its DRs are direct transcriptional targets of P53 and related stress mediators (37). As a consequence, combining conventional drugs and netrin-1 interference increases tumor cell death *in vitro* and potentiates tumor growth inhibiting effect *in vivo*, thus suggesting that, even when tumors do not express high levels of netrin-1, a combination of conventional drugs plus drugs inhibiting netrin-1–receptors interaction could amplify the chemotherapy-induced response. As discussed above, netrin-1 may not only have a pro-oncogenic effect by blocking the death induced by DCC or UNC5H, it may also activate "protumorigenic" pathways, as recently shown by the implication of the YAP pathway (38), thus further strengthening the rationale for moving netrin-1 interference into the clinic. A humanized monoclonal antibody disrupting netrin-1–receptors interaction is under preclinical development, with a clinical phase I scheduled for early 2016. This clinical evaluation will be crucial to validate or refute the importance of targeting DR pathways in cancer.

Interestingly, this first-in-class netrin-1 interfering compound may represent only one of a large family of drugs interfering with

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ligand–DR interaction. Indeed, not only netrin-1, but also other ligands of other DRs appear to be upregulated in cancer. NT-3 was also shown to be overexpressed in a fraction of neuroblastoma as a potential mechanism to block TrkC-induced apoptosis both *in vitro* and *in vivo* (39). Recently, Luchino and colleagues (4) elegantly demonstrated that PlexinD1 acts as a novel DR, and that its ligand, Sema3E, is upregulated in breast cancer. Using a Sema3E trap recombinant protein, they were able to demonstrate that Sema3E titration is associated with tumor growth and metastasis inhibition in different animal models.

The recent data obtained on the pair Hedgehog/CDON is also particularly challenging. Indeed, SHH signaling is believed to act as a pro-oncogenic pathway in many types of cancers (40). This has been formally demonstrated in cancers such as BCC or medulloblastomas, where mutations in the canonical pathway Ptch–Smo–Gli have been identified. However in most cancers, the implication of the HH pathway has been proposed because Hedgehog ligands—that is, SHH, DHH, or IHH—are upregulated and thought to act in a paracrine or autocrine manner on either tumor or stromal cells (40). Because of the current clinical failure of the Smo antagonists in solid cancers with hedgehog expression—as opposed to the clear beneficial effect in pathologies with mutations in the canonical pathway—and because of the description of a novel SHH receptor CDON as a DR (6), we have hypothesized that the effects of SHH overexpression in tumors is not simply to activate the canonical SHH pathway, but also to inhibit CDON-induced cell death. We have shown in different *in vitro* and *in vivo* models that silencing of SHH or systemic delivery of a recombinant protein interfering with SHH–CDON interaction (TRAP-SHH) is associated with tumor cell death *in vitro* and tumor growth inhibition *in vivo* through a mechanism dependent on CDON-induced apoptosis (6). Future clinical trials should compare whether a drug blocking SHH–CDON interaction—and thus triggering CDON-induced cell death—may be more efficient than Smo antagonists.

Questions Arising

These examples of ligand upregulation in tumors blocking apoptosis induced by their respective DRs likely represent just a tip of the iceberg, because it is expected that similar findings will be made on other existing or newly described DR–ligand pairs. One may wonder what will be the benefit of such treatment based on ligand–receptor disruption compared with other targeted treatments. Indeed, one would predict that by targeting ligand–receptor interaction, tumor cell clones selecting a loss of the receptor or of the downstream proapoptotic pathway should emerge similarly to the resistance mechanisms observed with kinase inhibitors. Yet, the difference here between kinase inhibitors and these ligand–receptor interfering agents is that, in the latter case, these drugs should actively trigger apoptosis, whereas the first action of the kinase inhibitors is to block the proliferative signals with an associated cell death by default (which in fact may be due to a DR effect, as described above). Moreover, it is tempting to consider the possibility that the interference of ligand–receptor may not only have an effect on tumor cells. The status of the stroma is probably of major importance. As an example, netrin-1 has been shown to regulate angiogenesis (41, 42), and possibly endothelial cell survival (43). Thus, blocking netrin-1 may not only promote tumor cell death but also mediate an antiangiogenic effect. Similarly, SHH was shown to promote survival of endothelial cells (44), so that blocking SHH–Ptc-CDON interaction may not only affect tumor cell death survival but also tumor-induced angiogenesis. To date, the relative importance of tumor cell death versus angiogenesis inhibition has not been assessed in the various animal models used to demonstrate the tumor growth-inhibiting effect of ligand-interfering agents. Similarly, we do not yet know whether all cancer cells in a single tumor are similarly sensitive to ligand-interfering agents. It is of interest to note that recent data have suggested that netrin-1 may be a survival factor to maintain pluripotency of embryonic stem cells (45). Would netrin-1 (and possibly other ligands of DRs) expressed in the tumor favor specifically the survival of cancer stem cells? If so, then treatment based on the ligand–DR interaction inhibition may not only affect tumor bulk, but also, and potentially preferentially, affect the very cells that are causally implicated in cancer relapse. Future basic research and clinical trials will have to evaluate how reactivating this death pathway could delay tumor relapse, and thus could be of benefit for patients.

Further to this latter aspect, the effect on metastasis is of course a fundamental issue. The DR paradigm states that a cell expressing a DR should undergo apoptosis unless the ligand is present, which offers new insights into the mechanism of metastasis. It could indeed be predicted that a cancer cell expressing a specific DR should be more prone to metastasis in tissues where the ligand of such DR is expressed. Such model has not been demonstrated directly, even though inhibition of DR-induced apoptosis has been shown to be associated with increased metastasis both for netrin-1 DRs and for PlexinD1 (4, 10, 34). Together with the view that cell death is a major regulator of metastasis (46), it will be interesting to see whether future studies demonstrate that the "seed-and-soil" theory for metastasis can integrate ligands of DRs as important components of the "soil," and whether drugs interfering with ligand–DR interaction may prevent metastasis development.

Disclosure of Potential Conflicts of Interest

P. Mehlen has ownership interest (including patents) in shares of Netris Pharma and is consultant/advisory board member for the same. No potential conflicts of interest were disclosed by the other author.

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