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REVIEW

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The multiple roles of Id-1 in cancer progression

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Abstract Id-1 (Inhibitor of differentiation/DNA binding) is a member of the helix–loop–helix protein family expressed in actively proliferating cells. It regulates gene transcription by heterodimerization with the basic helix–loop–helix transcription factors and therefore inhibits them from DNA binding and transactivation of their target genes. Early studies showed that Id-1 functions mainly as a regulator in cellular differentiation of the muscle cells. The oncogenic role of Id-1 was revealed recently by the finding that Id-1 expression was able to induce cancer cell growth and promote cell survival. In addition, Id-1 protein was frequently overexpressed in over 20 types of cancer, supporting its role in the tumorigenesis of a wide range of tissues. However, the fact that Id-1 was able to activate multiple pathways involved in tumor progression suggests that Id-1 may in addition function in promotion of tumor development. For example, overexpression of Id-1 was found to induce expression of MT1-MMP protein, leading to invasion of breast cancer cells. A close association between Id-1 expression and angiogenesis has also been demonstrated recently in both normal and cancer cells. Accordingly, in prostate cancer cells, expression of Id-1 was able to activate EGF-R and nuclear factor-κB activities and resulted in progression to androgen independence. In addition, in both nasopharyngeal carcinoma and prostate cancer cells, Id-1 expression was found to protect the cells from chemotherapeutic drug-induced apoptosis through regulation of the Raf-1/MAPK and JNK pathways. This review will discuss recent evidence supporting the role of Id-1 in tumor progression and the mechanisms involved.

Key words Id-1 · tumorigenesis · cancer progression

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Introduction

Id-1 (Inhibitor of differentiation/DNA binding) belongs to the Id protein family which consists of four members (Id-1 to Id-4). Id-1 (as well as other Id proteins) contains a well-conserved helix–loop–helix (HLH) domain that binds to the basic HLH (bHLH) proteins (such as members of the E-proteins family) (Benezra et al., 1990). As most of these bHLH proteins are transcription factors involved in activation of differentiation, dimerization with Id-1 resulted in inhibition of both their transactivation function as well as cellular differentiation (Benezra et al., 1990). Therefore, early studies on Id-1 have focused on its role in the regulation of cellular differentiation. For example, Id-1 has been shown to control the differentiation of muscle (Benezra et al., 1990), neurons (Lyden et al., 1999), mammary (Desprez et al., 1995), and B (Sun, 1994) and T-cells (Sun, 1994; Yan et al., 1997).

Recently, Id-1 has also been implicated as an oncogene which may play role in the tumorigenesis of a wide range of cancers. For example, aberrant expression of Id-1 has been reported in over 20 types of cancer (Wong et al., 2004). Moreover, Id-1 has been shown to regulate events such as cellular senescence (Alani et al., 1999, 2001; Ohtani et al., 2001), cell growth (Ling et al., 2002; Swarbrick et al., 2005), and cellular survival (Ling et al., 2003), which were frequently deregulated during cancer development. In addition, a number of the Id-1-downstream targets, such as Egr-1 (Ling et al., 2002) or bcl-xL (Ling et al., 2003), have been demonstrated to play critical roles in the carcinogenesis of certain type

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of cancers. These findings strongly supported the oncogenic role of Id-1 in cancer development. While the role of Id-1 in tumorigenesis has been studied extensively, the function of Id-1 in cancer progression has just started to be explored. Progression of cancer normally involves multiple steps including angiogenesis, invasion and metastasis. At least in several types of cancer, Id-1 expression was found to be associated with activation of angiogenesis (Lee et al., 2004; Ling et al., 2005) and induction of cancer cell invasion (Lin et al., 2000; Takai et al., 2001). In addition, the level of Id-1 expression was also found to be closely associated with tumor stage and poor prognosis in certain type of cancers (Schindl et al., 2001; Ouyang et al., 2002a; Schoppmann et al., 2003). How Id-1 may promote tumor progression in a particular type of cancer is still unclear, but results from several of recent studies have provided clues to the underlying mechanisms. This review will discuss some of the recent findings supporting the role of Id-1 in cancer progression. The potential mechanisms contributing to Id-1-induced cancer progression will also be discussed.

The discovery of the oncogenic role of Id-1

The first study that linked Id-1 to tumorigenesis was done by Alani et al. (1999), who showed that constitutive expression of Id-1 in keratinocytes resulted in induction of cell proliferation, inhibition of cellular senescence and differentiation, extension of life span and eventually cell immortalization. As aberrant cell proliferation and deregulation of senescence and differentiation are the hallmarks of tumorigenesis, these results provide the first evidence suggesting an oncogenic role of Id-1 in human cancer development. Subsequently, aberrant Id-1 expression was detected in dysplastic lesions as well as in pancreatic cancer (Maruyama et al., 1999). Since then, Id-1 overexpression has been reported in a wide range of cancers which include breast (Lin et al., 2000), colon (Wilson et al., 2001), and prostate cancer (Ouyang et al., 2002a), suggesting that up-regulation of Id-1 is commonly associated with tumorigenesis of different tissues.

Recently, the mechanisms responsible for the effect of Id-1 have been investigated extensively, and it is thought that a number of signaling pathways can be activated or inhibited by overexpression of Id-1. For example, in prostate cancer cells, overexpression of Id-1 was found to induce serum-independent cell growth through inactivation of the p16/RB tumor suppressor pathway (Ouyang et al., 2002b). In addition, the Raf-1/MAPK pathway was also found to be activated by Id-1 protein, leading to promotion of cell growth and cellular survival (Ling et al., 2002). Furthermore, the nuclear factor-κB (NF-κB) pathway, a downstream target of the Id-1 protein (Ling et al., 2003), was found to be constitutively activated in many cancer cells. These pathways are likely to be essential for the function of Id-1 in tumorigenesis.

Role of Id-1 in tumor invasion

Interestingly, in a number of cancers, Id-1 expression was also found to correlate with the disease progression. For example, in prostate cancer, expression of Id-1 was found to associate strongly with elevated Gleason grading and poor differentiation status of the cancer tissues (Ouyang et al., 2002a). Likewise, expression of Id-1 in cervical and breast cancer was shown to correlate with poor clinical outcome of the patients (Schindl et al., 2001; Schoppmann et al., 2003). In addition, the increase in aggressiveness of the ovarian cancer was also found to be associated with a higher Id-1 expression level (Schindl et al., 2003). These results suggested that Id-1 may function as a promoter in the tumor progression of certain cancers.

Tumor progression involves invasion of cancer cells into adjacent or distal regions, leading to metastasis of the original tumor. This involves detachment of tumor cells, breakdown of the basement membrane and extracellular matrix (ECM) surrounding the tumor, migration of tumor cells into the blood stream, attachment and further invasion into the target tissues and eventually proliferation of the tumor cells in the metastatic site. The matrix metalloproteinases (MMPs) represent a major protein family that regulates the degradation of basement membrane and the remodeling of the ECM. The MMP family is a group of zinc-binding endopeptidases which degrade the major components (e.g., collagens, glycoproteins) of the basement membrane and the ECM (Egeblad and Werb, 2002). This family consists of a total of 24 members, which are either secreted or membrane bound (Egeblad and Werb, 2002). The expression and functioning of MMP proteins are essential in many physiological processes such as embryonic development (Nagase, 1997) or the branching morphogenesis of the mammary gland at puberty as well as during pregnancy (Talhouk et al., 1991).

During cancer progression, a number of MMPs, such as MMP2, MMP9 or MMP14 (also known as MT1-MMP), were consistently found overexpressed in cancer cells (Shiomi and Okada, 2003). For example, expression of the MT1-MMP was found to correlate with the progression of breast, gastric, or thyroid cancer (Shiomi and Okada, 2003). Likewise, elevated expression of MMP7 was found to be associated with the metastasis of the colon (Gu et al., 2005) as well as liver cancer (Ogawa et al., 2005). The up-regulation of these MMPs was believed to facilitate the breakdown of the basement membrane and the

ECM, allowing the infiltration of the cancer cells during cancer cell invasion. Interestingly, using a mouse mammary epithelial cell line, Desprez et al. (1998) demonstrated that constitutive expression of Id-1 resulted in up-regulation of a novel MMP protein that is expressed during the involution of the mammary gland. Meanwhile, the expression of this 120 kDa MMP protein was strongly associated with the increase in motility and invasiveness of the mammary cells (Desprez et al., 1998). In addition, screening of breast cancer cell lines revealed that expression of Id-1 as well as the 120 kDa MMP protein was directly correlated with the invasiveness of these cell lines (Desprez et al., 1998), suggesting that Id-1 could regulate MMP protein as well as cell invasion. Accordingly, transfection of the Id-1 gene into the non-invasive breast cancer cell lines resulted in increase of cell proliferation as well as cell invasiveness. In addition, *in vivo* studies have revealed that high level of Id-1 expression was associated with tumor invasion as well as disease progression in both breast (Lin et al., 2000) and endometrial (Takai et al., 2001) carcinomas. Recently, the mRNA and protein levels of Id-1 was also found to increase with metastasis of breast cancer cells to the lung (Minn et al., 2005), suggesting that Id-1 may play an important role in mediating tumor metastasis.

Importantly, the invasion and metastatic ability of breast cancer cell have been shown to be suppressed significantly by down-regulating Id-1 expression through antisense or small interfering RNA (siRNA) treatment (Fong et al., 2003; Minn et al., 2005). Even more striking was the finding that the *in vivo* delivery of an Id-1 antisense expression vector into the highly metastatic breast cancer cells not only resulted in down-regulation of the MT1-MMP protein expression, but also led to suppression of cancer metastasis in xenografts (Fong et al., 2003). These results provided strong evidence that Id-1 positively regulates tumor invasion during cancer progression through up-regulation of the MMP proteins (for summary, see Fig. 1), and demonstrated for the first time that inactivation of Id-1 may have potential therapeutic value against metastatic breast cancer.

Role of Id-1 in tumor angiogenesis

Angiogenesis is an essential step in tumor progression, which provides additional blood supply necessary for the continuous expansion of the primary tumor as well as for the development of metastasis. The process of angiogenesis involves the destruction of the extracellular matrix of the existing blood vessel, migration and proliferation of the endothelial cells and eventually the formation of new endothelial tubes by the endothelial cells (Sato, 2003). Over the past few decades, a number of factors such as hypoxia inducible factor (HIF) (Brahimi-Horn and Pouyssegur, 2005); hepatocyte growth factor (HGF) (Rosen et al., 1997); and members of the vascular endothelial growth factor (VEGF) family (Carmeliet, 2005) have been identified to be associated with tumor angiogenesis during cancer progression.

Two separate studies on Id-1 knock-out mice revealed that Id-1 expression is required not only for the normal angiogenesis during embryogenesis, but is also essential for the tumor-associated angiogenesis during cancer progression (Lyden et al., 1999; Volpert et al., 2002). For example, loss of capillary branching and sprouting were observed in the developing brain in Id-1/Id-3 double knock-out mice. When tumor xenografts were implanted into these mutant mice, decreased tumor growth as well as loss of metastasis were observed, which were associated with impaired neovascularization of the tumor (Lyden et al., 1999). Using Id-1 knock-out mice, Volpert et al. (2002) made a similar observation, which was associated with up-regulation of a potent angiogenic inhibitor thrombospodin-1 in the Id-1 null embryonic fibroblasts. As Id-3 function was intact in these mutant mice, the result indicated that inactivation of Id-1 alone was sufficient to impair tumor angiogenesis (Volpert et al., 2002).

Interestingly, as reported by Lyden et al. both VEGF and its receptor were down-regulated in endothelial cells of the Id-1/Id-3 double knock-out mice (Lyden et al., 1999), suggesting a possible linkage between Id-1 and VEGF functioning. Indeed, a recent study carried out in our laboratory has demonstrated that VEGF is a

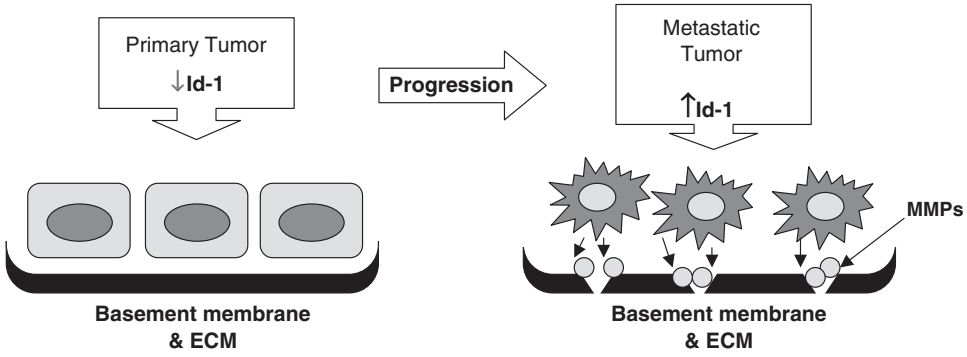

Fig. 1 The functions of Id-1 (Inhibitor of differentiation/DNA binding) in tumor invasion. The increased in Id-1 expression during cancer progression resulted in up-regulation of the matrix metalloproteinases proteins (i.e., MT1-MMP) in cancer cells which degrade the basement membrane and the extracellular matrix (ECM) surrounding the tumor. This facilitates the escape of the cancer cells to the circulation, leading to tumor metastatsis.

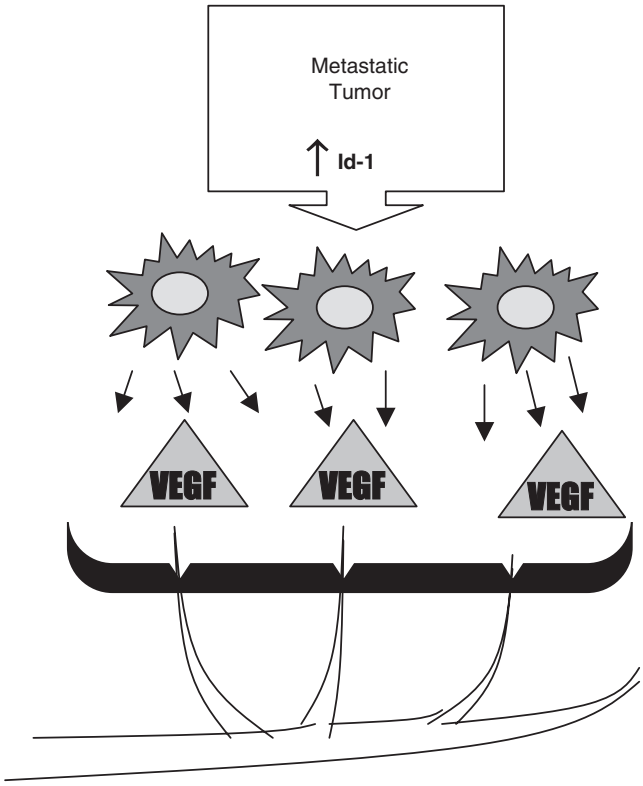

Fig. 2 The proposed mechanism for Id-1-induced tumor angiogenesis. In metastatic tumors, Id-1 expression results in up-regulation of vascular endothelial growth factor (VEGF) expression, leading to increase of VEGF secretion by the cancer cells. The increase in VEGF protein secretion in turn promotes the motility and the mobilization, proliferation as well as tube formation of the endothelial cells, leading to neovascularization of the tumor. Id-1, Inhibitor of differentiation/DNA binding.

downstream target of the Id-1 protein (Ling et al., 2005). As reported in that study, ectopic expression of Id-1 in a prostate cancer cell line that expresses low levels of both Id-1 and VEGF protein resulted in significant increase in VEGF secretion by the cells (Ling et al., 2005). This induction of VEGF production was associated with increased VEGF gene transcription, as evidenced by up-regulation of VEGF promoter activity after Id-1 gene transfection (Ling et al., 2005). In *in vitro* angiogenesis assays, the increase in VEGF observed in Id-1 transfectants promoted the growth and tube formation of the endothelial cells, which emphasized the role of Id-1 in angiogenesis (Ling et al., 2005). This interpretation was further supported by inactivation of the Id-1 with siRNA transfection, which resulted in down-regulation of both VEGF gene transactivation and protein secretion (Ling et al., 2005). As VEGF is one of the most potent tumor angiogenic factors that can activate not only endothelial cells proliferation, but also the blood vessel formation, these findings provide solid support for the role of Id-1 in induction of tumor angiogenesis (for summary, see Fig. 2).

Role of Id-1 in the development of hormone refractory cancer

Unlike other malignancies, the progression of breast and prostate cancer typically involves the development of hormone refractory disease. At this stage, the cancer no longer depends on hormonal stimulation for their survival and proliferation. As hormonal ablation therapy is the main treatment option available for advanced stage breast and prostate cancer patients, the development of hormone refractory cancer is the main reason for the treatment failure and the high mortality rate associated with both breast and prostate cancer. Extensive studies have focused on understanding the mechanism responsible for progression to hormone refractory disease. Mechanisms such as up-regulation of insulin-like growth factor-1 (Papatsoris et al., 2005) and epidermal growth factor-R (EGF-R) (Kaplan et al., 1996) have both been suggested to contribute to the androgen independent growth of the recurrent prostate cancer tumor. Meanwhile, constitutive activation of MAPK (Oh et al., 2001; Oka et al., 2005) and NF-κB (Zhou et al., 2005) activities has also been detected in both hormone-independent prostate and breast cancer cells in the hormone refractory stage.

Interestingly, Lin et al. (2000) have shown that exogenous Id-1 expression in the T47D hormone-dependent breast cancer cell line resulted in loss of estrogen dependency. Accordingly, transfection of Id-1 into the T47D cells resulted in significant growth stimulation in the absence of estrogen (Lin et al., 2000). In addition, while proliferation of the parental cells was responsive to estrogenic treatment in a dose-dependent manner, Id-1 transfectants failed to respond to the same estrogen dosage (Lin et al., 2000). These results suggest that the effect of estrogen on cell growth can be partially substituted by ectopic expression of the Id-1 protein.

Similarly, in a recent study we have demonstrated that transfection of an Id-1 expression vector into LNCaP androgen-dependent prostate cancer cells resulted in an androgen-independent phenotype (Ling et al., 2004). These Id-1 transfectants not only showed a decrease in responsiveness to androgenic stimulation, but were also found to express PSA in the absence of androgen (Ling et al., 2004), thus mimicking androgen-independent prostate cancer cells found in recurrent prostate cancer patients after androgen ablation therapy. Interestingly, constitutive activation of both of the Raf-1/MAPK and NF-κB activities, as well as up-regulation of EGF-R gene transcription and protein expression have been detected in the LNCaP Id-1 transfectants (Ling et al., 2004), suggesting that Id-1 may contribute to the progression of prostate cancer to androgen-independent stage through regulation of multiple pathways.

Our findings were further confirmed by the observation that Id-1 was highly up-regulated in tumors from recurrent prostate cancer patients when compared with that of patients bearing metastatic prostate cancer (Li et al., 2004; Ling et al., 2004), suggesting that the Id-1 overexpression may be responsible for the development of hormone refractory stage. More importantly, in a prostate cancer xenograft model, we found that Id-1 was significantly elevated in the cancer cells after androgen ablation (Ling et al., 2005). Although the exact mechanism for this up-regulation of Id-1 after androgen ablation is not clear, a recent screen revealed Id-1 to be a target gene downstream of the androgen receptor, which was down-regulated by androgenic stimulation in prostate epithelial cells. Based on these observations, it is reasonable to speculate that the increase in Id-1 after androgen ablation may be due to the removal of a suppressive signal exerted by androgen on the prostate cancer cells. This may in turn benefit the cancer cells by maintaining their growth and survival through activation of signaling pathways like Raf-1/MAPK, or NF-κB or both and eventually may promote the development of androgen independent prostate cancer. Nevertheless, further investigation is necessary to reveal the exact role of Id-1 in the progression of prostate cancer to androgen independent stage.

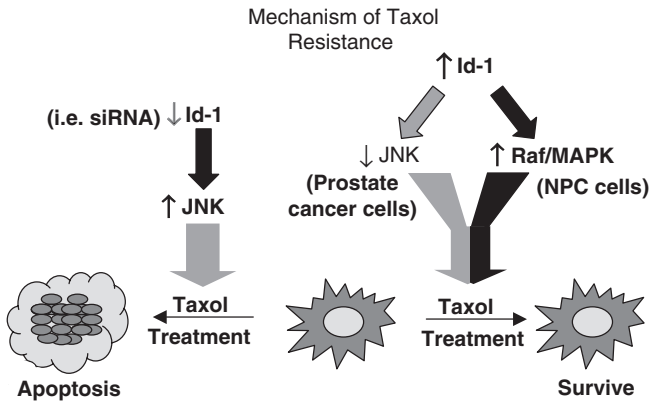

Fig. 3 Regulation of Taxol sensitivities of the cancer cell by Id-1 (Inhibitor of differentiation/DNA binding). Expression of Id-1 in cancer cells results in Taxol resistance through the activation of the Raf/MAPK (in NPC cells) and inactivation of JNK pathway (in prostate cancer cells). On the other hand, down-regulation of Id-1 expression results in activation of the JNK pathway and sensitizes the cancer cells to Taxol-induced apoptosis. NPC, nasopharyngeal carcinoma.

Role of Id-1 in the development of chemotherapeutic drug resistance

Chemotherapy is a widely used treatment against metastatic cancer which induced cellular apoptosis through specific mechanisms. Although these chemotherapeutic drugs are effective in killing many types of cancer cells, disease recurrent after the treatment is frequent due to the development of drug resistance. These recurrent tumors are highly resistant to further chemotherapy and are usually associated with a more aggressive phenotype. Therefore, understanding the mechanism for the development of drug resistance is essential for improving the effectiveness of chemotherapy. Until now, a number of factors or pathways have been identified that contribute to drug resistance in cancer cells. For example, up-regulation of p-glycoprotein has been shown to be responsible for development of multi-drug resistance in a variety of cancers (Lehne, 2000). Alternatively, up-regulation of apoptosis inhibitors such as Bcl-2 (Kim et al., 2004) has also been associated with chemotherapeutic drug resistance. In addition, deregulation of signaling pathways such as Raf-1/MAPK (Davis et al., 2003), NF-κB (Nakanishi and Toi, 2005) or the JNK (Vasilevskaya and O'Dwyer, 2003) pathway has been demonstrated to inhibit chemotherapeutic drug-induced apoptosis in cancer cells.

The fact that Id-1 can activate both Raf-1/MAPK and NF-κB pathways (Ling et al., 2002, 2003) has led to the hypothesis that Id-1 may also contribute to development of drug resistance. Indeed we have demonstrated in both prostate and nasopharyngeal carcinoma (NPC) cells that ectopic Id-1 expression was able to confer resistance to Taxol treatment (Cheung et al., 2004; Zhang et al., 2005). For example, in the NPC cells, Id-1 expression was found to activate the Raf-1/MAPK pathway through induction of the Raf-1 and MEK-1 phosphorylation (Cheung et al., 2004). This activation of Raf-1/MAPK by Id-1 was found to be associated with the decrease in sensitivities of the NPC cells to Taxol-induced apoptosis (Cheung et al., 2004). Accordingly, inactivation of the Raf-1/MAPK in the Id-1 transfectants by a MEK-1 inhibitor was able to restore drug sensitivity of the NPC cells (Cheung et al., 2004), suggesting that Raf-1/MAPK activation is essential for the Id-1 induced Taxol resistance.

While the Taxol resistance of the NPC cells may be mediated through the Raf-1/MAPK pathway, the inhibition of JNK activation by Id-1 was found to be responsible for the increased Taxol resistance observed in prostate cancer cells (Zhang et al., 2005). As shown in two prostate cancer cell lines, PC-3 and DU145, down-regulation of Id-1 by siRNA treatment not only resulted in induction of JNK activation, but also lead to sensitization of both cell lines to Taxol treatment (Zhang et al., 2005). In addition, these effects can both be reversed by treating the cells with the JNK-specific inhibitor, indicating that in prostate cancer cells, the JNK pathway is associated with the protective role of Id-1 against Taxol-induced apoptosis (Zhang et al., 2005).

In addition to Taxol resistance, a recent study revealed that up-regulation of Id-1 was also associated with resistance of prostate cancer cells to doxorubicin

and cyclophosphamide treatment (Lin et al., 2005). Whether Id-1 may play a role in multi-drug resistance is still not clear at the moment, but these findings provide strong evidence that Id-1 overexpression may protect cancer cells from apoptosis induced by chemotherapeutic drugs through regulation of multiple signaling pathways (for summary, see Fig. 3).

Conclusion

In summary, Id-1 appears to be involved in the promotion of cancer progression through regulation of multiple pathways. Firstly, Id-1 is found to up-regulate MMP proteins as well as the invasion of the cancer cells (Desprez et al., 1998; Lin et al., 2000), which are necessary for the breakdown of the barrier (i.e., basement membrane and the ECM) that restrains the tumor growth and metastasis. In addition, Id-1 has been shown to promote tumor angiogenesis through induction of the VEGF gene transcription and protein expression (Ling et al., 2005), leading to proliferation and endothelial tube formation of the vascular endothelial cells. On the other hand, in breast and prostate cancer cells, Id-1 has been demonstrated to induce the hormone-independent phenotype, which is a critical step in the progression of the breast and prostate cancers. Finally, Id-1 is able to protect the cancer cells from apoptosis induced by the chemotherapeutic drugs (Cheung et al., 2004; Lin et al., 2005; Zhang et al., 2005), leading to the development of drug resistance. Overall, Id-1 functions as an essential factor for providing the nutrients (i.e., angiogenesis and EGF-R activation), the force (i.e., invasion) as well as the protection (i.e., resistance to apoptosis) that are necessary for tumor progression. Since inhibition of tumor invasion, angiogenesis as well as enhancement of drug sensitivities of the tumor are currently the main novel strategies for improving the treatment of cancer, the versatile role of Id-1 in regulating all these processes make it an attractive therapeutic target in developing new therapeutic strategies for the management of cancer progression as well as for the treatment of cancer at advanced stage.

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