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Editorial

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NDRG1: a novel therapeutic target against metastatic cancers

Abstract

Tumor metastasis is a critical clinical problem that requires urgent attention. Recently, there has been growing interest in the development of metastasis suppressor proteins as targets for anti-cancer therapy. N-myc downstream regulated protein 1 (NDRG1) is an important and well established metastasis suppressor protein that has shown promise as a significant therapeutic target to inhibit cancer metastasis. Notably, a novel series of thiosemicarbazone-based anti-cancer agents under development have shown the ability to up-regulate NDRG1. Therefore, further studies examining the effect of NDRG1 as a therapeutic target to prevent cancer metastasis are warranted.

Volume 1 Issue 1 - 2015

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Received: April 29, 2015 | **Published:** May 08, 2015

Cancer metastasis

Cancer metastasis is the process by which tumor cells spread from the primary tumor to distant locations. It is one of the major clinical problems and accounts for about 90% of cancer related deaths.[1] Metastasis is a complex process and involves multiple steps.[2]

i. Local invasion–Cells undergoes the epithelial mesenchymal transition (EMT) and locally invades through the basement membrane.

ii. Intravasation-Tumor cells actively transverse through the walls of capillaries and lymphatics into the circulation.

iii. Transport-Cancer cells are transported to different sites, and if they survive the hostile conditions during transport, they adhere to solid supporting tissue and form micro-thrombi.

iv. Extravasation-Cancer cell micro-thrombi invade into distant tissue, typically lungs, brain, bone or liver.

v. Formation of micro-metastasis-After extravasation, cells lodge at secondary sites, where they must proliferate and colonize for successful metastasis. These metastatic processes are controlled by number of promoters and suppressors, which orchestrate a complex array of events to achieve successful metastasis.[1] Recently, there has been growing interest in the role of metastasis suppressor genes, which have been shown to inhibit the formation of successful metastasis. To date, a number of metastasis suppressors have been identified, such as NDRG1, SSeCKs, KAI1 etc.[3] These genes are generally found to be suppressed in advanced tumors and form an attractive target for the development of novel therapeutics.

NDRG1: A novel target against cancer metastasis

The *NDRG1* (also known as *RTP, Drg1, cap43, rit42, PROXY-1*) gene encodes the well-known metastasis suppressor protein, NDRG1. It belongs to the NDRG family of proteins, with NDRG-2, -3 and -4 forming the other members of the family. The gene encodes a 3kb mRNA, which translates a 43kDa protein. NDRG1 is known to be down-regulated in number of cancers, such as breast, prostate, ovarian, etc.[4,5] In fact, studies have shown that there is an inverse relationship between the severity of the tumor and NDRG1 levels, whereby lower levels of NDRG1 were observed in bio-specimens from more advanced and aggressive tumor stages.[5]

Although the exact mechanism through which NDRG1 exerts its anti-metastatic effects is still not completely understood, significant progress has been made in this direction in past few years. Interestingly, Chen et al.[6] have shown that NDRG1 can inhibit EMT *via* its ability to modulate the tumor growth factor-β (TGF-β) pathways. In fact, NDRG1 increased the membrane expression of E-cadherin,[6] which is an important protein required for cell-cell adhesion.[7] NDRG1 was also shown to suppress the TGF-β-induced SMAD signaling pathway,[6] which also plays a critical role in EMT.[8]

The WNT/β-catenin pathway is another important known regulator of the EMT.[9] Recent studies have shown that NDRG1 can inhibit WNT-dependent signaling, leading to the suppression of EMT.[10,11] Collectively, these investigations indicate that inhibition of EMT by NDRG1 is one of the important mechanism *via* which it can inhibit cancer cell metastasis. Cancer cell migration is another integral step in successful metastasis of cancer cells.[1] Studies by Sun et al.[12] demonstrated that NDRG1 can suppress the Rho-associated coiled-coiled containing protein kinase 1 (ROCK1)/phosphorylated myosin light chain 2 (pMLC2) pathway.[12] In fact, ROCK1/pMLC2

is involved in formation of actin stress fibers, which are required for cellular migration.[13,14] Thus, inhibition of ROCK1/pMLC2 pathway by NDRG1 could directly lead to inhibition of cellular migration, and thus, metastasis.[12]

Src is an important promoter of cancer metastasis, which is known to exert a variety of effects on the metastasis-invasion cascade through a number of downstream regulators.[15] Significantly, it has been shown to down-regulate E-cadherin,[16] which itself is known to be a metastasis suppressor.[3,7] Moreover, Src is also known to increase cell migration *via* its downstream effector molecules, such as p130Cas.[17] A recent study by Liu *et al.*[18] demonstrated that NDRG1 can inhibit the pro-metastatic effects of Src, leading to a phenotype with reduced metastatic ability. Collectively, these studies indicate that NDRG1 interacts with number of critical molecules involved in cancer metastasis and thus, exerts a multi-faceted anti-metastatic effect. Further studies are required to completely understand how this important metastasis suppressor interacts with other crucial players in the complex metastatic process.

Thiosemicarbazone anti-cancer agents

Importantly, a novel series of thiosemicarbazone anti-cancer agents have been demonstrated to up-regulate NDRG1.[19] These agents are shown to act *via* a double punch mechanism, leading to:

i. Chelation of essential metal ions, such as iron and copper.

ii. Formation of redox active iron and copper complexes.[19–21]

Importantly, these ligands have potent and selective anti-tumor activity, both *in vitro* and *in vivo*.[22–24] The lead compound di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemicarbazone (DpC) has demonstrated potent anti-tumor activity *via* oral as well as i.v. administration *in vivo*. It has also been shown that DpC has a very safe drug profile at the optimal doses required for effective anti-tumor activity.[22,23] Notably, DpC has been recently been commercialized and will enter clinical trials in 2015.

It has been shown that NDRG1 was required for the activity of these thiosemicarbazones.[11] In fact, there was a marked decrease in the anti-metastatic activity of these agents in breast cancer cells which were silenced with NDRG1, compared to cells with normal levels of NDRG1.[11] Notably, thiosemicarbazone anti-cancer agents have also been shown to mediate similar effects as mediated by NDRG1 on number of pathways involved in cancer metastasis such as the TGF-β-induced EMT[6] ROCK1/pMLC2 mediated formation of stress fibers for cellular migration[12] and Src-mediated pro-metastatic pathway.[18]

Future directions

NDRG1 has shown promise for development as an anti-metastatic drug target. The advancement of thiosemicarbazones as potential clinical agents, *via* their ability to up-regulate NDRG1, has opened a new opportunity for establishment of novel anti-metastatic therapies. In summary, further research is required to comprehensively understand the mechanisms *via* which NDRG1 exert its metastatic suppressive effects.

Acknowledgements

D.R.R. thanks the National Health and Medical Research Council of Australia (NHMRC) for a Senior Principal Research Fellowship and Project Grants. S.S. thanks Sydney Medical School for an Early Career Research Grant. D.S.K. thanks the NHMRC for a Project Grant [1048972] and a NHMRC RD Wright Fellowship [1083057].

Conflict of interest

D.R.R. is a stakeholder in the companies, Oncochel Therapeutics LLC and Oncochel Therapeutics Pty Ltd., that are developing the thiosemicarbazone, DpC, for the treatment of cancer. D.R.R. also consults for Oncochel Therapeutics LLC and Pty Ltd.

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Citation: Sahni S, Merlot A, Jansson P, et al. NDRG1: a novel therapeutic target against metastatic cancers. Int Clin Pathol J. 2015;1(1):1–3.
DOI: 10.15406/icpjl.2015.01.00001