The dependence receptor notion: from a cell biology paradigm to alternative anti-cancer therapies

Patrick Mehlen

Research Cancer Center of Lyon
Centre Léon Bérard
Rue Laennec, Lyon, France

A few years ago, we proposed an original concept of cell biology: whereas the classic dogma postulates that transmembrane receptors are inactive unless bound by their specific ligand, they proposed that some receptors may be active not only in the presence of their ligand, but also in their absence. In this latter case, the signaling downstream of these unbound receptors leads to apoptosis. These receptors were consequently named "dependence receptors", as their cell expression renders the cell's survival dependent on the presence in the cell environment of its respective ligand. We proposed that this dual function could lead these receptors to have key roles both during embryonic development and in the regulation of tumorigenesis.

In the context of cancer, the hypothesis is that these receptors are tumor suppressors that would limit tumor progression by inducing apoptosis of tumor cells outside of settings of ligand accessibility/availability. We are particularly interested in the receptors that bind netrin-1-i.e., DCC and UNC5H-. We showed that both DCC and UNC5H are dependence receptors in cancer cells: whereas in the presence of their ligand netrin-1, they transduce classic "positive" signals, in the absence of netrin-1, they actively trigger apoptosis. Interestingly, DCC and UNC5H are now considered as tumor suppressors because their expression is lost in many cancers, suggesting that the presence of these receptors is a constraint for tumor progression. This was actually formally proven by showing that the invalidation of UNC5H3 or the overexpression of netrin-1 in the digestive tract of mice resulted, in a similar reduction of apoptosis and a similar increased tumorigenesis. Thus, aggressive cancers that develop are cancers for which the dependence receptor pathways are blocked through mechanisms including the genetic loss of these receptors.

However, a loss of dependence receptors is not always the selective advantage used by tumor cells to escape this survival dependence on the presence of the ligand. Indeed, we showed that in many cancers such as metastatic breast cancer, lung cancer or neuroblastoma, tumor cells acquire the preferred autocrine expression of netrin-1. This selective advantage for the tumor is much more appealing in terms of therapeutic strategy. Indeed, the titration of the ligand by a molecule that interferes on the interaction between a dependence receptor and its ligand should lead to tumor cell death. Along this line, we showed that titration of netrin-1 by a drug candidate allows tumor cell death in vitro and triggers regression of tumors and metastases in mice. Of interest, this gain of ligand is probably not limited to netrin-1 but may possibly be extended to the other ligands of other dependence receptors. Thus, we are now trying to develop drugs based on the interference on the interaction between dependence receptors and their ligands as anti-cancer strategies. The first human trials (Phase I) using an agent interfering between netrin-1 and its receptors should begin in late 2013. Thus, from a basic cell biology concept, our laboratory may, within the next few years, provide new tools to fight against cancer with a wide societal impact.

Patrick Mehlen
Apoptosis, Cancer and Development
Research Cancer Center of Lyon
E-mail: patrick.mehlen@lyon.unicancer.fr

EDUCATIONS/TRAINING

1989-93:	Student of the 'Grande Ecole: Ecole Normale Supérieure'
1989-92:	'Magistère de Biologie Moléculaire et Cellulaire (LYON)' (Equivalent to Master in Biochemistry, Molecular and Cellular Biology)
1992-95:	Ph. D. Thesis, University Claude Bernard, Lyon, France.
2000:	'Habilitation à diriger les recherches'

POSITIONS AND HONORS

>2011-date:	Director of the Laboratoire of Excellence DEVweCAN, Lyon
>2011-date:	Deputy Director of The Research Cancer Center of Lyon.
>2009-date:	Co-Director of the Institute for Clinical Science, Centre Léon Bérard
>2007-date:	Adjunct Professor at the Buck Institute for Age Research, Novato, USA
>2007-2011:	Director of the laboratory "Apoptosis, Cancer and Development"- CNRS UMR5238, Centre Léon Bérard, Lyon, France.
>2004-2006:	Research Director of the unit "Apoptosis, Cancer and Development"- CNRS FRE2870, CGMC, Lyon, France.
>1998-2004:	Group leader of the "Apoptosis and Differentiation" Laboratory - CNRS UMR5534, CGMC, Lyon, France.
>1997-1998:	Sabbatical within the Burnham Institute for Medical Research, program on "Aging and Cell Death"- CA, USA.

-1999	Bronze Medal CNRS
-2002	Laureate of the Schlumberger Principal Prize
-2004	Laureate of the Tartois Prize
-2004	Laureate of the Grand Prix Curie-Jeanne Loubaresse
-2005	Silver Medal CNRS
-2006	Laureate of the Grand Prix EuroCancer
-2007	Laureate of the Prix Charles Oberling
-2007	Laureate of the Prix Ruban Rose <<Grand Prix de la Recherche>>
-2007	Laureate of the Prix Del Duca de Cancérologie (Académie des Sciences)
-2009	Laureate of Grand Prix de l' Innovation "Universal Biotecs"
-2010	The Pius XI Gold Medal from Pontificia Academia Scientiarum City of Vatican
-2011	Laureate of the Grand Prix Bettencourt-Schueller pour les Sciences du Vivant
-2006	EMBO Member since
-2006	Adjunct Professor at the Buck Institute For Age Research, since

RECENT PUBLICATIONS

1. Fombonne J, Bissey PA, Guix C, Sadoul R, Thibert C, and P. Mehlen. (2012) Patched dependence receptor triggers apoptosis through ubiquitination of caspase-9. ***Proc Natl Acad Sci USA***. 109(26):10510-5. Epub 2012 Jun 7.
2. Castets M., Broutier L., Molin Y., Brevet M., Chazot G., Gadot N., Paquet A., Mazelin L., Jarrosson-Wuilleme L., Scoazec J.Y., Bernet A. & P. Mehlen (2012). DCC constrains tumor progression via its dependence receptor activity. ***Nature***. 482(7386):534-7.
3. Mehlen P., Delloye-Bourgeois C., and A. Chedotal (2011). Novel roles for Slits and netrins: axon guidance cues as anti-cancer targets? ***Nature Rev. Cancer***. 11:188-97
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5. Mille F., Thibert C., Fombonne J., Rama N., Guix C., Hayashi H., Corset V., Reed JC, and P. Mehlen (2009). The Patched dependence receptor triggers apoptosis through a DRAL-caspase-9 complex. ***Nature Cell Biology*** 11, 739-46.
6. Castets M., Coissieux M.M., Delloye-Bourgeois C., Bernard L., Delcros J.G, Bernet A., Laudet V. and P. Mehlen (2009). Inhibition of endothelial cell apoptosis by netrin-1 during angiogenesis. ***Dev. Cell*** 16, 614-620.
7. Fitamant J., Guenebeaud C., Coissieux M.M, Guix C., Treilleux I., Scoazec J.Y., Bachelot T., Bernet A., and P. Mehlen (2008). Netrin-1 expression confers a selective advantage for tumor cell survival in metastatic breast cancer. ***Proc. Natl. Acad. Sci. USA*** 105, 4850-5.
8. Mehlen P., Puisieux A (2006). Metastasis: a question of life or death. ***Nature Rev. Cancer***. 6, 449-458.
9. Mazelin L., Bernet A., Bidaud-Bonod C., Pays L., Arnaud S., Gespach C., Bredesen D.E., Scoazec J.Y., and P. Mehlen. (2004) Netrin-1 controls colorectal tumorigenesis by regulating apoptosis. ***Nature*** 431, 80-84.
10. Thibert C., Teillet M.A., Lapointe F., Mazelin L., LeDouarin, N., and P. Mehlen (2003) Inhibition of neuroepithelial patched-induced apoptosis by sonic hedgehog. ***Science*** 301:843-6.