Editorial

The dependence receptor notion: another way to see death

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It has been known for over half a century that cells depend for their survival on stimulation that is mediated by various receptors and sensors. For example, cells may require specific soluble trophic factors, cytokines, hormones, extra-cellular matrix interactions, cell–cell interactions, or electrical activity for survival. In each case, withdrawal of the stimulus leads to apoptosis. It has generally been assumed that this occurs through the loss of the associated positive survival signals, such as Akt phosphorylation. While such survival signals are clearly very important, data obtained over the past 10 years argue for a complementary and novel form of signal transduction, which induces apoptosis and is activated by stimulus withdrawal. This 'negative signal transduction' is mediated by specific 'dependence receptors', which induce apoptosis only in the absence of the required stimulus (e.g. when unbound by a trophic ligand). Thus, the expression of various dependence receptors creates states of dependence on their respective ligands.

From a very dubitative – and should we confess, sometimes aggressive – attitude towards this notion, for example, (i) 'how dare you even think that an unbound receptor could be active', (ii) 'everything about cell death following trophic factor withdrawal is known: a default program due to kinases-dependent pathways being shut off', or (iii) 'your data are simple artifacts of cell culture and protein overexpression' – we are slowly moving towards a more respectable view, maybe. The reason for this gain of interest is clearly due to the fact that from pure *in vitro* studies using immortalized cells,^{1,2} this notion has recently been supported by studies in animals models.^{3,4}

However, there are many ramifications to the dependence receptor theory: for example, the expression of dependence receptors ties cells to a specific context, in which the ligand is available, and therefore may serve to block metastatic spread of neoplasms or growth beyond local ligand availability. Another example of the effects of dependence receptors is the mediation of developmental cell death in cells that do not receive trophic factor support. Therefore, dependence

receptors often play a dual role, both as tumor suppressors and mediators of neuronal development. Indeed, the vast majority of the dependence receptors isolated so far has been shown to be involved in neuronal navigation and in the regulation of cancer progression. This special issue will deal with the different aspects of the duality of dependence receptors. Firstly, Dale E Bredesen and colleagues will present an overview of the notion of dependence receptors and discuss the nature of the different dependence receptors isolated so far.⁵ They will review what is known about the mechanisms these receptors use to trigger cell death, and how this implicates them in nervous system development, cancer progression, and neurodegenerative diseases. Hirofumi Arakawa will then sign an exciting review on a specific set of dependence receptors, the netrin-1 receptors DCC and UNC5H.⁶ He will show how a guidance cue for commissural neurons – that is, netrin-1 – and its receptors DCC and UNC5H have recently been shown to constitute ligand/receptors pairs that control tumor progression possibly in connection with the p53 tumor suppressor. As there seemed to be a clear link between dependence receptors, neuronal navigation and cancer, Alain Chedotal and colleagues will present an overview of axon guidance-related molecules and how these molecules, which are expressed in adult tissues, are also involved in cancer.⁷ We will end this special issue with a review by Dwayne Stupack, who will describe a recently identified set of dependence receptors, integrins.⁸

As usual, the reading of these reviews will raise more questions than they actually answer. What is the relation between integrins and DCC, molecules that do not display much sequence similarity? How large is this dependence receptor family, which rather looks like a functional group of receptors sharing a similar function? Nonetheless, the claim of a proapoptotic unbound receptor is starting to emerge and together, a putative new vision of tumor suppressor gene function. How this can help the development of therapeutic strategies against cancer and possibly other diseases is now a thrilling question.

1. Rabizadeh S *et al.* (1993) *Science* 261: 345–348
2. Mehlen P *et al.* (1998) *Nature* 395: 801–804
3. Thibert C *et al.* (2003) *Science* 301: 843–846
4. Mazelin L *et al.* (2004) *Nature* 431: 80–84
5. Bredesen DE *et al.* (2005) *Cell Death Differ.* 12: 1031–1043
6. Arakawa H (2005) *Cell Death Differ.* 12: 1057–1065
7. Chedotal A, Kerjan G and Moreau-Fauvarque C (2005) *Cell Death Differ.* 12: 1044–1056
8. Stupack D (2005) *Cell Death Differ.* 12: 1021–1030