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Laboratory of Cell Differentiation

Haematopoietic and neural cell differentiation



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Research topics

In the body the brain is the most cholesterol-rich organ. Despite this, remarkably little is known about the mechanisms in the brain that regulate cholesterol homeostasis. Due to the blood-brain barrier, plasma lipoproteins are unable to traverse and instead cholesterol must be synthesized *de novo* from within the CNS. Thyroid hormone receptors, activated in response to thyroid hormone (T3), are known to modulate the level of serum cholesterol via complex regulatory pathways. By screening for T3-regulated genes we have identified Disp3, a sterol-sensing domain-containing protein that is related to the Dispatched family of proteins. Analysis by RT-PCR and immunohistochemistry demonstrated that DISP3 is predominantly expressed in specific cell types of the brain, retina and testis. DISP3 localizes within the endoplasmic reticulum and was further found to co-localize with cholesterol (Fig. 1). Ectopic expression of DISP3 in fibroblasts resulted in elevated cholesterol levels combined with an altered cholesterol distribution. We propose that DISP3 represents a new molecular link between thyroid hormone and cholesterol metabolism in the brain.

We have also identified, cloned and characterized the first non-mammalian Tpo, chicken thrombopoietin, and its receptor c-Mpl (2). Discovery of chicken Tpo and c-Mpl will greatly facilitate future studies regarding thrombocytic differentiation (Fig. 2) and haematopoietic stem cell development. Moreover, we have introduced an experimental model of chicken bi-potent thrombo/erythropoietic progenitors that can be used to identify key regulators of cell fate determination (2).

Current grant support

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Selected recent papers

1. Karafiat V, Dvorakova M, Krejci E, Kralova J, Pajer P, Snajdr P, Mandikova S, Bartunek P, Grim M, Dvorak M. Transcription factor c-Myb is involved in the regulation of the epithelial-mesenchymal transition in the avian neural crest. *Cell Mol Life Sci.* 2005;62:2516-2525.
2. Bartunek P, Karafiat V, Bartunkova J, Pajer P, Dvorakova M, Kralova J, Zenke M., Dvorak M. Impact of chicken thrombopoietin and its receptor on hematopoietic cell development. *Exp Hematol.* 2008; 36:495-505.

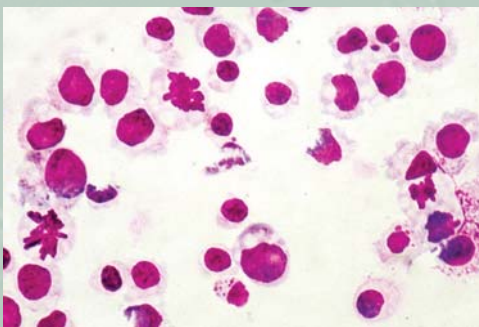


Fig. 2. Thrombocytic progenitors sorted from chicken bone marrow and cultivated in the presence of recombinant chicken Tpo. Several thrombocytic cells and various stages of development including the dividing cells are shown.

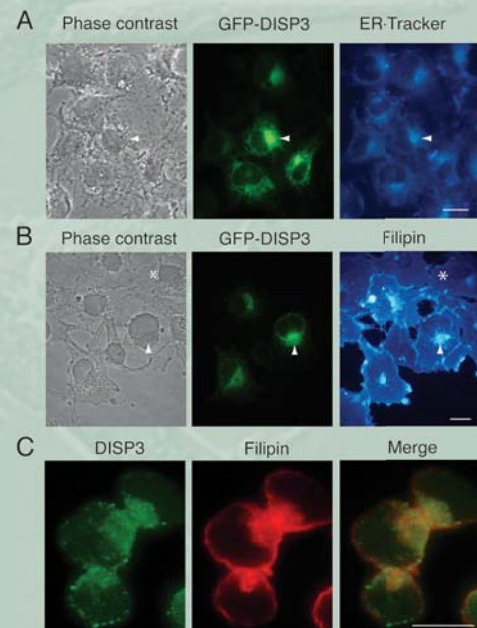


Fig. 1. DISP3 localizes to the ER and co-localizes with cholesterol. COS7 cells transiently transfected with GFP-DISP3 were labelled with (A) an ER-Tracker dye to show the sub-cellular localization of DISP3 and (B) filipin to visualize cellular cholesterol. Arrowheads highlight selected DISP3-GFP-transfected cells; asterisks mark non-transfected cells. (C) Y79 cells were stained with Disp3 antibody (green) and filipin (red-pseudocoloured). Yellow staining represents areas of co-localization.