NOTCH1 as a Potential Therapeutic Target in Cutaneous T-cell Lymphoma

The paper by Kamstrup et al. provides a significant step forward in the development of new therapeutic principles in how to manage advanced mycosis fungoides. The paper highlighted here describes a new therapeutic target in cutaneous lymphoma: receptor Notch.

The following is a summary of a recently published paper by Kamstrup et al. The reference for the whole article is the following: *Kamstrup MR, Rahbek Gjerdrum LM, Biskup E, Thyssing Lauenborg B, Ralfkiær E, Woetmann A, Ødum N, Gniadecki R. NOTCH1 as a Potential Therapeutic Target in Cutaneous T-cell Lymphoma. Blood 2010; 116: 2504–2512.*

Advanced cutaneous lymphomas, such as mycosis fungoides, present a formidable therapeutic challenge. In its earliest stage mycosis fungoides is relatively easy to control with skin-directed therapies, such as psoralen plus ultraviolet A (PUVA), topical steroids, or electron beam radiation. However, progression to the tumour stage is associated with poor prognosis. There are no effective chemotherapies for advanced mycosis fungoides. Gemcitabine or doxorubicin-based treatment regimes provide only short-term remissions, and relapses are exceedingly difficult to manage. The development of new therapeutic principles is therefore an area of urgent medical need.

Notch is expressed ubiquitously in different cell types, but its major role is the regulation of T-cell development. Mice with mutated Notch are unable to produce mature T cells. In humans, constitutive activation of Notch is oncogenic, resulting in T-cell leukaemias. Notch has subsequently been shown to act as an oncogene in different leukaemias and solid cancers.

Kamstrup et al. demonstrated that Notch is expressed in mycosis fungoides in a stage-dependent manner (the higher the clinical stage the more Notch-positive cells are found on lymphoma cells). Kamstrup subsequently used various cell lines derived from cutaneous T-cell lymphomas to explore the effects of Notch inhibition. Deletion of Notch by the small interfering RNA approach resulted in cell cycle stop and apoptosis of lymphoma cells. Interestingly, Notch inhibition could also be achieved by small chemical molecules, the gamma-secretase inhibitors (GSIs). GSIs was originally developed for treatment of Alzheimer's disease, but it has subsequently been shown that these compounds also inhibit Notch. The mechanism of action is the blockage of the proteolytic step in the activation cascade of Notch. Kamstrup et al. screened a number of different GSI compounds and found one that showed a very high potency *in vitro* for producing apoptosis in lymphoma cell lines.

The findings of Kamstrup et al. may have immediate clinical relevance. Different GSI compounds are currently undergoing clinical trials in oncology. Experience from the clinical use of GSIs can be translated directly into the field of cutaneous lymphoma and may result in the emergence of new treatment modalities.

Maria R. Kamstrup, is a PhD student at the Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark. She received her medical degree at the University of Copenhagen in 2004. Her research interest is therapy of cutaneous lymphomas, with a focus on radiotherapy and development of novel treatment approaches.

Robert Gniadecki, Country Editor, Denmark
University of Copenhagen, Bispebjerg Hospital, Bispebjerg bakke 23, DK-2400 Copenhagen NV, Denmark. E-mail: r.gniadecki@gmail.com