Prognostic value of DAXX/ATRX loss of expression and ALT activation in PanNETs: is it time for clinical implementation?

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Pancreatic neuroendocrine tumours (PanNETs) originate from the islets of Langerhans of the pancreas and they represent almost 3% of all pancreatic tumours. Over 50% of patients present nodal or distant metastasis at time of diagnosis, which results in an estimated 5-year survival in 27% of cases. On the contrary, localised well-differentiated PanNETs, especially those <2 cm, have a more indolent behaviour with 5 years survival of 93% of patients. 

Death domain-associated protein (DAXX) and or alpha-thalassemia/mental retardation X-linked chromatin remodeler (ATRX) are mutated in almost 40% of sporadic PanNETs, often in combination with MEN1 mutations. DAXX/ATRX mutations result in loss of nuclear expression of the protein in the tumour tissue. DAXX and ATRX loss highly correlates with alternative lengthening telomeres (ALT) activation, although a causal role is still under investigation.

Mechanisms driving PanNETs progression on DAXX and ATRX loss are still poorly understood. While the molecular mechanisms associated with DAXX and ATRX loss are still elusive, a clear role in PanNETs prognosis is emerging.

In the present work, Hackeng et al consolidated the prognostic relevance of DAXX and ATRX loss in PanNETs, using a multicentre collective including 561 patients with PanNET. In multivariate analysis including tumour grade, lymph vascular invasion, perineural invasion, tumour stage, regional lymph node metastasis, loss of DAXX/ATRX expression and the presence of ALT, both loss of DAXX/ATRX and ALT activation were found independent prognostic factors for relapse free survival (p<0.001 for both).

While, in non-metastatic PanNETs DAXX/ATRX loss and ALT activation clearly indicated a shorter disease free survival, in metastatic samples ALT activation seems to have an opposite role. Metastatic patient with ALT positive
The reasons for this different behaviour are not clear yet, additional mutations may take over during the progression or different response to treatments may play a role. Indeed, ALT positive tumours showed highcopy number variation (CNV), which may results in a more sensitivity to specific therapies. Additional investigations in this respect are crucial to identify the potential Achille’s heels of these tumours. While the role of DAXX/ATRX loss for prognosis is now widely recognised, it is still to clarify if it could a have a predictive function as well. Currently, in fact, there is no way to select a specific therapy for this subtype of tumours; more studies in this direction are essential.

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**REFERENCES**