

EACR - 20 Poster Prize Winners

EACR-20 Poster Prizes were awarded on three consecutive days at the Anniversary Meeting. Sponsored by the Pezcoller Foundation, the awards were presented by Professor Gios Bernardi who also spoke about the Pezcoller Foundation at the Opening Ceremony



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Role of Cancerous Inhibitor of Protein Phosphatase 2A (CIP2A) in Gastric Carcinogenesis.

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Gastric cancer is the second most common cause of cancer related deaths worldwide (Parkin DM *Cancer J Clin.* 2005; 55(2):74-108.). Even though excision in toto of the neoplastic tissue forms the mainstay of the management against this tumour, the five year survival rate for gastric cancer is still 20-30% (Dicken BJ *Ann Surg.* 2005;241(1):27-3) Therefore, there is obvious need to identify new diagnostic markers and therapeutic modalities against this

deadly form of cancer.

Protein Phosphatase 2A (PP2A) is a human tumour suppressor which inhibits the activity of several oncogenic signalling pathways. Recent experimental evidence has established that inhibition of PP2A activity is a prerequisite for human cell transformation (Arroyo JD and Hahn H. *Oncogene* 2005; 24, 7746-7755)). However, the mechanisms by which PP2A tumour suppressor activity is inhibited in human cancer are poorly understood. CIP2A protein (alias KIAA1524 and p90) was recently identified as a human oncoprotein which functions to stabilize transcription factor c-Myc at the protein level by inhibiting PP2A-mediated c-Myc dephosphorylation (Junttila MR *Cell.* 2007;130(5):51-62.). Overexpression of CIP2A has been detected in gastric adenocarcinoma, colon adenocarcinoma and head and neck squamous cell carcinomas (HNSCC; Junttila et al, Soo Hoo L *Oncogene.* 2002; 21(32):5006-5015)

Few studies have delineated the functional role of c-Myc and its regulation in gastric cancer. Interestingly, less than 20% of gastric cancers with c-Myc protein over expression display c-Myc gene amplification (Mitsui F *Mod Pathol.* 2007; 20(6):622-631). Therefore, other mechanisms by which c-Myc is regulated, may contribute towards gastric carcinogenesis. These mechanisms could involve increased stability of the protein via interference with mechanisms regulating c-Myc proteolytic degradation (Junttila and Westermarck *Cell Cycle.* 2008; 7(5):592-6). Importantly, the relevance of c-Myc stabilizing

mechanisms in human gastric cancers is yet to be demonstrated.

In our project we have attempted to address these questions by investigating expression and role of c-Myc stabilizing protein CIP2A in gastric carcinogenesis. We demonstrate the prognostic role of CIP2A in gastric cancer patients along with its role in promoting cell proliferation and c-Myc stability in gastric cancer cells. Interestingly, we identified c-Myc expression as the first mechanism stimulating CIP2A expression in cancer cells, thereby establishing a positive feedback mechanism between the two human oncoproteins. To strengthen these findings we have used alternate approaches like chemical inhibitor of Myc-Max dimerization and mouse embryo fibroblasts (MEFs) expressing switchable c-Myc (MycER), to verify the role of c-Myc as CIP2A expression stimulator. Additionally, co-expression of both human oncoproteins was shown in human gastric cancer specimens, further highlighting the existence of a positive feedback loop between the two human oncoproteins.

In conclusion, results of our work demonstrate for the first time the clinical relevance of CIP2A in a human cancer. Identification of CIP2A as a c-Myc target protein also provides novel insights into understanding how c-Myc could autoregulate its own stability in malignant cells. Finally, results of this study suggest that inhibition of c-Myc stabilizing mechanisms could provide a therapeutic opportunity to inhibit c-Myc protein expression in cancer, without interfering with c-Myc gene expression in normal tissues.



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sequence, giving a strong indication for additional proteolytic processing of ILEI. The cleaved form was not detectable in whole cell extracts. In ILEI cleavage assays using purified full length protein we found, that ILEI was cleaved extracellularly, mostly by serum proteases.

To investigate the role of ILEI processing, we generated a series of mutant ILEI forms with the hope being defective in proteolytic cleavage. Using these mutants in overexpression studies we could identify essential amino acids for proteolytic cleavage and secretion. Some mutants were defective in proteolytic processing but not in secretion and we found one mutant which was neither cleaved nor secreted. Surprisingly, all overexpressed non-cleavable ILEI forms were able to induce EMT, including the non-secretable form.

These findings show first, that proteolytic cleavage is not essential for ILEI secretion, providing additional support for extracellular processing of the protein. Secondly, these data indicate that proteolytic processing is not required for ILEI action, raising the question, if full length ILEI might have higher biological activity than the cleaved form. Finally and most unexpectedly, these data show that a sole intracellular action of ILEI can induce EMT in vitro. Currently, we are investigating the capacity of these mutant ILEI forms for metastasis induction, to reveal if autocrine or paracrine functions of this cytokine are required for tumour progression.

ILEI, an essential cytokine for tumour progression: how does it act?

ILEI (Interleukin-like EMT Inducer) is essential for tumour formation and progression in a murine mammary epithelial cell model. Stable expression of ILEI in EpH4 and EpRas cells caused EMT, tumor growth and metastasis. RNAi-mediated knock-down of ILEI in EpRas cells before and after EMT (EpRasXT) prevented and reverted TGFbeta-dependent EMT, also abrogating metastasis formation.

ILEI (FAM3C) belongs to the FAM3 family of secreted cytokines. Thus, the simplest explanation for the effects of ILEI overexpression in epithelial cells might be an autocrine action of the secreted protein. However, it was difficult so far to show this with purified recombinant ILEI. Our aim is to understand the way of ILEI action and find possibilities for potential therapeutic interference with the pathway.

Initially, Western blot analysis showed that the secreted form of the ILEI protein is smaller in size than intracellular ILEI. Mass Spec data confirmed the lack of 17 amino acids at the N-terminus in addition to the signal peptide



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The day began like a normal congress day in the EACR meeting celebrated this time in Lyon, just until my boss appeared in the room where we were attending one session and asked me to check out my poster and...It was a great surprise as I was not expected to find the Pezcoller Poster Award on my board.

After those months since summer I can say that I feel very proud about receiving the prize, not only because of the personal scientific recognition, but also about what the prize means: to promote scientific research against cancer, guaranteeing a continuous contact with the international oncological community worldwide.

I am conscious that a huge number of researchers deserved also the Pezcoller Poster award, that is why I would like it if it could represent the hard effort of each scientist that works day-by-day trying their best to reduce the burden of human cancer.

Thank you for supporting cancer research and aiming to make it easier for all of us!

Poster Prizes Sponsored by the Pezcoller Foundation were awarded on three days during the EACR-20 Conference

