8th International Conference on Protein Crosslinking and Transglutaminases (September 01-04, Lübeck, Germany)

CONCLUDING REMARKS

The 1st Conference on Protein Crosslinking and Transglutaminases was held in Miami, in 1988 (organized by *Peter Davies, Paul Birckbichler and Laszlo Fesus*) and it was a big success. This was followed by several equally successful ones in Cannes, 1990 (*Uwe Reichert and Rainer Schmidt*); in Ardmore, 1992 (*Paul Birckbichler*); in Debrecen, 1994 (*Laszlo Fesus*); in Cheju Island, 1996; (*Ron Chung, Sang-Chul Park, In-Gyu Kim*); in Lyon, 2000 (*Said El Alaoui and Gerard Quash*); in Ferrara, 2002 (*Carlo Bergamini*).

The Lübeck conference was organized by *Rolf Hilgenfeld* in a very professional way, with outstanding care and friendly hospitality. The choice of the conference site (Media Docks) was excellent and the 175 attendees enjoyed the atmosphere of both the city of Lübeck and the high quality of science (see the program at *www.pcl8.biochem.uni-luebeck.de*).
Regarding the scientific presentations the following points may be emphasized.

1. **The issues and basic research have never been in the history of transglutaminase conferences so close to the clinics as it was in Lübeck. FXIII polymorphism was linked to disorders (*Robert Ariens*), data on FXIII a and b subunit knock out mice has provided new insights to the human deficiency of this coagulation factor (*Akitada Ichinose*) . Several examples of transglutaminase (TG) action on hetero-dimeric G-protein receptors in vascular and neurodegenerative diseases have been presented (*Ursula Quitterer*). It is becoming more and more clear that extracellular action of transglutaminases has a significant role in fibrosis in the kidney and at other sites (*Tim Johnson, Takahito Ito*)). New TG2 variant has been described in pancreatic beta cells (*Elisabetta Verderio-Edwards*) . Involvement of TG5 in the pathogenesis of a rare skin disease (aural peeling skin syndrome) was demonstrated (*Eleonora Candi*). It was reported that in Candida infections buccal surface transglutaminase covalently crosslinks hyphal wall protein of Candida albicans to epithelium mediating its adherence and invasion *Paula Sundstrom*). New aspects of the crucial role of TG2 in the initiation of the symptoms of coelic disease have been revealed (*Ilma Korponay-Szabo, Ludvig Sollid, Walburga Dieterich)*. It was shown that the role of transglutaminases in neurodegeneration may be related to its cross-linking as well as signalling functions (*Gerda Adringa, Zoltan Nemes*). TG2 can promote drug resistance and metastasis of tumor cells (*Kapil Mehta*) and matrix changes induced by this enzyme modulate tumor growth (*Martin Griffin*).**
2. **It is clear that although we have learnt a lot we still need many new structural informations about transglutaminases to understand their mechanism of action. Several reports at the conference have advanced our knowledge including the recognition of the substrate binding of FXIII (*Muriel Maurer*), description of the fibronectin binding site of TG2 (*Alexey Belkin*), the demonstration of the relaxed and compact form of TG2 in relation to its two steps activation mechanism (*Siiri Iismaa*), the identification of new Ca-binding sites of TG2 (*Robert Kiraly and Laszlo Fesus*), alternative activation mechanisms of transglutaminases (*Carlo Bergamini*) such as the one elicited by TIG3 on TG1 (*Richard Eckert*).**

3. **While the presence of transglutaminase have been newly demonstrated in organisms such as shrimps (*Meng-Yi Chen*) and plants (*Jose Torne, Stefano Del Duca and Donatela Serafini-Fracassini*), several members of the transglutaminase family were shown to have overlapping roles in many mammalian tissues and biological systems. One clear example is the skin, where almost all members of the TG family play some roles in its different biological functions. It was also shown at the conference that the angiotensin receptor is croslinked by both FXIIIa and TG2 in some cells under pathologic conditions (*Ursula Quitterer*) and both of these two enzymes seem to contribute to chondrocyte and osteoblast differentiation as well as mineralization (*Maria Nurminskaya, Mari Kaartinen*). TG1, TG2 and FXIII play significant roles in the colon in various physiological and pathological settings (*Giuseppe D'Argenio*).**
4. **Transglutaminase 2 still remained quite a secretive and enigmatic enzyme while some novel functions have been revealed. Recent results have demonstrated that TG2 can participate in functions which leads to opposite fates of cells: activation of its transamidating activity is usually pro-apoptotic while its G-protein signalling capability rather provides a pro-survival effect in various kinds of cells - including protection against death signals such as Fas-mediated killing and participation in the engulfment of apoptotic cells (*Laszlo Fesus and Zsuzsa Szondy*). Its localization on the cells surface by binding to integrins and fibronectin also mediates cell survival, although integrins are not necessarily needed for this (*Martin Griffin*). TG2 may also play a role, by its protein disulphide isomerase activity, in maintaining mitochondrial oxydative phosphorylation and ATP production (*Mauro Piacentini*). It contributes to granulocyte differentiation by modulating gene expression (*Zoltan Balajthy*) and forms a complex with vascular endothelial growth factor receptor modulating endothelial response (*Rima Dardik*)**
5. **The use of transglutaminases in biotechnology is increasing with remarkable new applications. New expression systems have been developed such as in baculovirus (*In-Gyu Kim*), in tobacco leaves (*Angela Sorrentino and Loredana Mariniello*) . New wool fibers (*Joao Cortez and Martin Griffin*), gels (*Laretta Garde*), materials from renewable resources (*Markus Pietzsch*) have been made by transglutaminase-based technologies. The search for transglutaminase substrates has reached a more intense stage by in silico and phage display (*Yoshiaki Sugimura and Kiyotaka Hitomi, Eva Csosz and Laszlo Fesus*) techniques. In transglutaminase related diagnostics new assays have been developed including a quick test for coelic disease (*Ilma Korponay-Szabo*), novel colorimetric (*Philip Bonner, In-Gyu Kim*), immune-capture (*Said El Alaoui*) and scintillation-proximity (*Andras Madi*) assays have been developed and one utilizing the reverse action of transglutaminases, their isodipeptidase activity (*Martin Hils and Ralf Pasternack)* . Specific antibodies have been produced against cross-linked proteins (*Soichi Kojima*)**
6. **The synthesis of new types of transglutaminase inhibitors, including those which act specifically on one member of this enzyme family, have made it possible to probe the consequences of in vivo inhibition of these enzymes (*Chaitan Khosla, Martin Griffin*). Reports at the conference showed encouraging results in the inhibition of transglutaminase activities in tissues, though it looks that the new inhibitors, similarly to previous ones, can not penetrate cells. Nevertheless, it became clear in Lübeck that the pharmacological utilization of transglutaminase**

inhibitors has entered into a new phase with possible applications in fibrosis, celiac sprue , cancer and neurodegenerative disease.

In summary, the 8th conference has been a huge success and contributed very significantly to advancing the field of transglutaminase research.

Contributed by Laszlo Fesus
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