



## Διαλέξεις

ΠΕΜΠΤΗ 15 ΜΑΡΤΙΟΥ 2007

ΑΙΘΟΥΣΑ: «ΑΜΦΙΘΕΑΤΡΟ»

ΩΡΑ: 11.30-12.00

ΣΥΝΤΟΝΙΣΤΗΣ: ΚΑΣΤΑΝΑ ΟΥΡΑΝΙΑ

### NEW APPROACHES FOR COMPLEX WOUNDS: THE VIEW OF A SURGEON

LUC TÉOT

President of World Wound Healing Society

Complex wounds have for a long period of time been given to surgeons, as there was no other issue than surgery. In many cases, surgery failed and the patient was more or less abandoned to medical doctors.

One of the key element is to have a multidisciplinary approach of complex wounds. The surgeon alone cannot solve the numerous difficulties as:

- The nutritional status: under a level of serum albumin of 25, chances to heal whatever be the solution proposed are minimal. This is the moment of renutrition program, not for surgery.
- The infection status: local infection can be evident, but there is a number of cases when an infection is latent and difficult to manage. This critical colonization situation should be assessed and treated with adapted dressings, prior to any surgical procedure
- The vascularization of the tissues involved in the surgical procedure. Many surgeons consider there is a few places for surgery in devitalized tissues. However, since the emergence of distal bypasses and the technical capacities of specialists to recanalize vessels, surgery can be anticipated, with solutions less aggressive than the amputations proposed before. Distal and economic resection of bone, joints or segments of foot are now common, when combining vascular bypass surgery, the use of adapted antimicrobial dressings, the use of negative pressure therapy and the use of limited covering procedure, like skin grafts or limited flaps.

This new combination of techniques, including new modes of debridement less aggressive on the tissues, can help in managing complex wounds using limited surgery, a good strategy of debridement of necrotic tissues followed by an adapted use of covering techniques.

ΑΙΘΟΥΣΑ: «ΑΜΦΙΘΕΑΤΡΟ»

ΩΡΑ: 12.00-12.30

ΣΥΝΤΟΝΙΣΤΗΣ: ΔΙΑΜΑΝΘΗ ΣΟΦΙΑ

### 1. "SIGNALING EVENTS REGULATING FIBROBLAST FUNCTIONS IMPORTANT FOR WOUND HEALING: ROLE OF GROWTH FACTORS – IMPLICATIONS FOR PHARMACOLOGIC INTERVENTION"

ALAIN MAUVIEL - INSERM U697, Paris, France

The JNK group of MAP kinases, also known as stress-activated

kinases, are activated upon exposure of cells to cytokines, growth factors, and environmental stresses such as UV irradiation or heat shock. In the nucleus, JNKs phosphorylate transcription factors such as c-Jun, a process that leads to maximal transcriptional activity of the latter. We used both a gene knockout approach and pharmacologic modulation to elucidate the specific roles played by the Jun-N-terminal kinase (JNK) and NF-κB pathways downstream of TNF-α in the context of α(2) type I collagen gene (COL1A2) expression. In *jnk1<sup>-/-</sup>jnk2<sup>-/-</sup>* double-knockout fibroblasts (*jnk<sup>-/-</sup>*), TNF-α inhibited basal COL1A2 expression but had no effect on TGF-β-driven Smad-dependent gene transactivation unless *jnk1* was introduced ectopically. Conversely, in NEMO- (NF-κB essential modulator knockout) fibroblasts, lack of NF-κB activation did not influence the antagonism exerted by TNF-α against TGF-β but prevented repression of basal COL1A2 gene expression by TNF-α. Similar regulatory mechanisms take place in dermal fibroblasts, as evidenced using transfected dominant-negative forms of MKK4 and IKK-α, critical kinases upstream of the JNK and NF-κB pathways, respectively. Mechanistically, we identified JNK activation by TNF-β as favouring protein-protein interactions between Jun and Smad3 proteins, critical transcriptional mediators of TGF-β. Jun-Smad3 interactions preventing Smad3 binding to its cognate DNA cis-element(s) in target gene promoters, resulting in the interruption of Smad3-dependent transcription. These results represent a key demonstration of an alternate usage of distinct signaling pathways by TNF-α (NF-κB or JNK) to inhibit the expression of a given gene, COL1A2, depending on its activation state: JNK allows TNF-α to antagonize Smad-dependent COL1A2 gene expression while NF-κB represses basal COL1A2 expression.

Interestingly, we have then been able to identify the JNK pathway as essential to provide anti-fibrotic activities to a variety of pharmacologic drugs/compounds, including 5-fluorouracyl at non toxic concentrations, the immunosuppressive drug rapamycin, and the anticoccidial alkaloid halofuginone. Specifically, these drugs are able to both repress collagen gene expression and to activate that of metalloproteinases. Together, our work demonstrates that activators of the JNK pathway may represent interesting candidates for therapeutic intervention in conditions requiring accelerated extracellular matrix turnover and degradation, while JNK inhibitors may accelerate tissue repair.

### 2. "IMPLICATION OF THE JNK PATHWAY IN CELL MIGRATION AND WOUND REPAIR"

V.I. ALEXAKI

INSERM U697, Hôpital Saint-Louis, Paris, France

During wound healing the fibroblasts migrate throughout the wound and synthesize extracellular matrix, restoring skin integrity. Multiple cytokines, growth factors and their downstream signaling mechanisms control these events, one of which is transforming growth factor beta (TGF-β). Extracellular stimuli, including TGF-β, transduce their cellular signals through activation of the



mitogen-activated protein (MAP) kinases, a group of which are the JNK proteins (JNK1, 2 and 3). The present work studied the implication of the JNK pathway in regulating fibroblast motility, capacity to contract mechanically unloaded collagen gels and expression of type I collagen. The study has been carried out in primary human dermal fibroblasts, in mouse embryo fibroblasts (wild type and *jnk*<sup>-/-</sup>) and in fibroblasts expressing mutated, and thus inactive, c-Jun (a phosphorylation substrate protein of JNK). *jnk*<sup>-/-</sup> fibroblasts or fibroblasts mutated for c-Jun, and human dermal fibroblasts in which JNK is being pharmacologically inhibited, display impaired wound closure capacity due to reduced migratory activity and altered contractility. Discrete molecular mechanisms were identified that directly implicate the transcription factors c-Jun and JunB to control these cellular responses. Together, this study clearly shows the importance of the JNK pathway for the function of fibroblasts in the process of tissue repair, involving cell migration, matrix contraction and collagen biosynthesis (Javelaud et al., JBC 2003).

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**ΩΡΑ: 11.30-12.00**

**ΣΥΝΤΟΝΙΣΤΗΣ: ΧΡΗΣΤΑΚΗΣ ΧΡΗΣΤΟΣ**

### **“MULTI- DISCIPLINARY/PROFESSIONAL APPROACHES IN WOUND HEALING. THE DANISH EXPERIENCE”**

#### **FINN GOTTRUP**

Professor of Surgery  
Copenhagen Wound Healing Center  
Department of Dermatology  
Bispebjerg Hospital, Copenhagen, Denmark

**Objective:** To improve prophylaxis and treatment of patients with all types of problem wounds. This is achieved during establishment of a multi-professional organisation in the primary as well as in the secondary health care sector.

**Methods:** Establish a multi-professional organisation in the health care sector consisting of hospital centres and smaller units in the primary health care sector. Collaboration models between the hospital and community sector should be developed and standardised treatment protocols and patient guidelines should be carried out. Evidence for improved quality of treatment and care and a standardised educational program for all involved types of staff should be accomplished.

**Results:** This type of model has been established in Denmark. Clinically the organisational model consist of two hospitals units with own staff and in-beds: Copenhagen Wound Healing Center started in 1996 and The University Center of Wound Healing started in 2003.

The referral policy has been simplified and centralised. Treatment plans including diagnostics, treatment and prevention have been optimised. Different types of educational services, basic and clinical research and prevention programs have been established. Collaboration models for relationship between the

hospital and community sectors are presently discussed.

A national education program of 6 months has been developed for nurses. Education of medical doctor to become experts in wound healing (2 years) has been achieved by the establishment of a national accepted expert area called “Clinical Wound Healing”.

Evidences based research will in the future be achieved using wound databases including socio-economical data. In Denmark a PC database primarily for patients with diabetic foot ulcers has been developed. This database is primarily for hospital use, but presently a program for pocket PC's used in the primary health care sector is under development.

**Conclusion:** The optimal way to deliver wound care in both the hospital- and community sector is still under evaluation. Development of organisational models including databases, systemic evaluation of quality of care and outcome measures may in the future give us the ideal and optimal method of organisation of wound care delivering. An advanced organisational model from Denmark is demonstrated.

Gottrup F et al. A new concept of a multidisciplinary wound healing center and a national expert function of wound healing. Arch Surg. 2001;136:765-72

Gottrup F. Optimizing wound treatment through health care structuring and professional education. Wound Rep Reg 2004; 12:129-133

Gottrup F. A specialised wound healing center concept: importance of a multidisciplinary department structure and surgical treatment facilities in the treatment of chronic wounds. Am J Surg 2004; 187:38-43S

Gottrup F. Management of the Diabetic Foot: Surgical and Organisational Aspects. Horm Metab Res, 2005;37, Supplement 1:69-75

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### **“EFFECT OF SILVER ON BURN WOUND INFECTION CONTROL AND HEALING: REVIEW OF THE LITERATURE”**

#### **ATIYEH S. BISHARA,**

Division Plastic and Reconstructive Surgery, American University of Beirut Medical Center, Beirut, Lebanon

Silver compounds have been exploited for their medicinal properties for centuries. At present, silver is reemerging as a viable treatment option for infections encountered in burns, open wounds, and chronic ulcers. The gold standard in topical burn treatment is silver sulfadiazine (Ag-SD), a useful antibacterial agent for burn wound treatment. Recent findings, however, indicate that the compound delays the wound healing process and that silver may have serious cytotoxic activity on various host cells. The present review aims at examining all available evidence about effects, often contradictory, of silver on wound infection control and on wound healing trying to determine the practical therapeutic balance between antimicrobial activity and cellular toxicity. The ultimate goal remains the choice of a