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新興降脂療法、新型藥物及其開發背後的科學原理

Emerging Lipid-Lowering Therapies & Mechanisms

時　　間：115 年 6 月 28 日(星期日) 08:30~12:00
地　　點：臺北榮民總醫院 致德樓第四會議室

08:30-08:35	***Opening Remarks***	胡啟民主任 Chii-Min Hwu
	座長：胡啟民主任 (Chii-Min Hwu)	
08:35-09:20	CRP 與動脈粥樣硬化：從臨床到基礎研究 CRP & Atherosclerosis: From Clinical to Basic	梁耀仁教授 Yao-Jen Liang
09:20-10:05	Bempedoic Acid：上游膽固醇合成抑制的新策略 Bempedoic Acid: Targeting Cholesterol Synthesis Upstream	裴駒主任 Dee Pei
10:05-10:25	***Coffee Break***	
	座長：胡啟民主任 (Chii-Min Hwu)	
10:25-11:10	PCSK9 抑制新時代：從 siRNA 到口服療法 PCSK9 Inhibition in the New Era: From siRNA to Oral Therapy	黃金洲主任 Chin-Chou Huang
11:10-11:55	ApoC-III 抑制在動脈粥樣硬化治療中的角色 ApoC-III Inhibition in the Treatment of Atherosclerosis	林肇鋒醫師 Chao-Feng Lin
11:55-12:00	***Closing Remarks***	胡啟民主任 Chii-Min Hwu

CRP & atherosclerosis: From clinical to basic

CRP 與動脈粥樣硬化：從臨床到基礎研究

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C-reactive protein (CRP), traditionally regarded as a nonspecific biomarker of systemic inflammation, has emerged as a pivotal mediator in the pathogenesis of atherosclerosis, bridging clinical observations with underlying molecular mechanisms. Epidemiological studies have consistently demonstrated that elevated CRP levels independently predict cardiovascular events, underscoring its clinical relevance beyond conventional lipid parameters.

At the cellular level, accumulating evidence indicates that CRP actively participates in vascular inflammation rather than serving merely as a passive marker. CRP promotes endothelial dysfunction, a key early event in atherogenesis, by inducing pro-inflammatory cytokines such as interleukin-6 and interleukin-8, and by upregulating adhesion molecules including vascular cell adhesion molecule-1 (VCAM-1) and monocyte chemoattractant protein-1 (MCP-1). These changes facilitate monocyte recruitment and adhesion to the endothelium, thereby accelerating plaque initiation and progression.

Mechanistically, CRP exerts its effects through Fcγ receptors, particularly CD32, leading to activation of intracellular signaling pathways such as nuclear factor-κB (NF-κB), a central regulator of inflammatory gene expression. This signaling cascade amplifies vascular inflammation and perpetuates a pro-atherogenic environment. Furthermore, CRP-mediated inflammation establishes a vicious cycle, enhancing cytokine release and sustaining endothelial injury.

From a translational perspective, targeting CRP-related pathways offers potential therapeutic implications. Modulation of inflammatory signaling, including inhibition of NF-κB activation, may attenuate endothelial dysfunction and atherosclerotic progression. Thus, CRP represents not only a clinically valuable biomarker but also a mechanistic link connecting systemic inflammation to vascular disease, highlighting its dual role in both risk stratification and pathophysiological insight.

Bempedoic Acid: Targeting cholesterol synthesis upstream

Bempedoic Acid：上游膽固醇合成抑制的新策略

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Bempedoic acid is a novel lipid-lowering agent that inhibits cholesterol biosynthesis upstream of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, offering an alternative therapeutic strategy for patients with hypercholesterolemia. It is a prodrug that is selectively activated in the liver by very long-chain acyl-CoA synthetase 1 (ACSVL1), thereby minimizing systemic exposure and reducing the risk of muscle-related adverse effects commonly associated with statins.

Mechanistically, bempedoic acid inhibits adenosine triphosphate–citrate lyase (ACL), a key enzyme involved in the conversion of citrate to acetyl-CoA, an essential precursor for cholesterol and fatty acid synthesis. By reducing hepatic cholesterol synthesis, it upregulates low-density lipoprotein receptor (LDLR) expression, thereby enhancing clearance of circulating LDL cholesterol (LDL-C).

Clinical trials have demonstrated that bempedoic acid, either as monotherapy or in combination with other lipid-lowering therapies such as statins or ezetimibe, produces a significant reduction in LDL-C levels, typically in the range of 15–25%. Notably, the CLEAR Outcomes trial showed that bempedoic acid significantly reduced major adverse cardiovascular events in statin-intolerant patients, highlighting its role in cardiovascular risk reduction.

In addition to lipid-lowering effects, bempedoic acid has been associated with modest reductions in high-sensitivity C-reactive protein (hs-CRP), suggesting potential anti-inflammatory benefits. Overall, bempedoic acid represents an important addition to the therapeutic armamentarium, particularly for patients who are unable to tolerate statins or require additional LDL-C lowering beyond conventional therapies.

PCSK9 inhibition in the new era: From siRNA to oral therapy

PCSK9 抑制新時代：從 siRNA 到口服療法

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a central regulator of low-density lipoprotein cholesterol (LDL-C) homeostasis through its promotion of hepatic LDL receptor degradation. Therapeutic targeting of PCSK9 has therefore become a highly effective strategy for cardiovascular risk reduction, particularly in patients with atherosclerotic cardiovascular disease (ASCVD) or those who fail to achieve lipid goals with conventional therapies. While monoclonal antibodies against PCSK9 have demonstrated substantial LDL-C lowering and cardiovascular benefit, recent advances have expanded the therapeutic landscape into novel modalities with improved convenience and durability.

Small interfering RNA (siRNA)-based therapy, exemplified by inclisiran, represents a major innovation by selectively silencing hepatic PCSK9 synthesis. Through sustained intracellular activity, inclisiran enables potent and durable LDL-C reduction with twice-yearly dosing, addressing long-standing challenges in treatment adherence. In parallel, the development of oral PCSK9 inhibitors marks a significant paradigm shift. MK-0616, a first-in-class orally bioavailable macrocyclic peptide, has demonstrated promising LDL-C–lowering efficacy in early-phase clinical trials, offering the potential to combine the potency of PCSK9 inhibition with the convenience of oral administration.

These advances signal a transition from injectable biologics to gene-silencing approaches and now toward oral therapeutics, reflecting a broader evolution in lipid management. This lecture will provide a comprehensive overview of the mechanistic foundations of PCSK9 inhibition, with a particular focus on inclisiran and emerging oral agents such as MK-0616, and will discuss their potential roles in optimizing long-term cardiovascular risk reduction in contemporary clinical practice.

ApoC-III inhibition in the treatment of atherosclerosis

ApoC-III 抑制在動脈粥樣硬化治療中的角色

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Apolipoprotein C-III (ApoC-III) has emerged as a critical regulator of triglyceride-rich lipoprotein (TRL) metabolism and a key contributor to atherogenesis. By inhibiting lipoprotein lipase activity and impairing hepatic uptake of TRL remnants, ApoC-III promotes hypertriglyceridemia and the accumulation of remnant particles, both of which are increasingly recognized as causal factors in atherosclerotic cardiovascular disease (ASCVD). Genetic and epidemiological studies have consistently demonstrated that loss-of-function variants in the APOC3 gene are associated with lower triglyceride levels and a reduced risk of cardiovascular events, thereby establishing ApoC-III as a compelling therapeutic target.

Recent advances in RNA-targeted therapies have enabled selective inhibition of ApoC-III synthesis. Antisense oligonucleotides (ASOs), such as volanesorsen and next-generation agents like olezarsen, as well as small interfering RNA (siRNA) therapies, have shown substantial reductions in circulating triglycerides and remnant cholesterol levels in patients with severe hypertriglyceridemia, including familial chylomicronemia syndrome. Beyond triglyceride lowering, emerging evidence suggests that ApoC-III inhibition may improve lipoprotein remnant clearance and attenuate vascular inflammation, thereby exerting direct anti-atherogenic effects.

This evolving therapeutic paradigm highlights the expanding role of targeting TRL metabolism in cardiovascular prevention. In this lecture, we will review the biological role of ApoC-III, summarize current clinical evidence for ApoC-III–targeted therapies, and discuss their potential implications in the management of residual cardiovascular risk beyond low-density lipoprotein cholesterol lowering.