

חזית המחקר בקרדיולוגיה מולקולרית

השתלמות לבוגרי התמחות בקרדיולוגיה

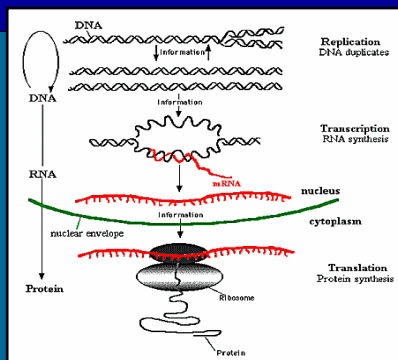
קיסריה, 8-11 בספטמבר 2004

ד"ר משה פליגלמן
מנהל מערך האשפוז
מערך קרדיולוגי
מרכז רפואי כרמל, חיפה

Presentation outline

- What is *molecular cardiology*?
- Principles and examples:
 - Genetics of diseases
 - Pathophysiology
 - Diagnostics
 - Therapeutics

Central Dogma of Molecular Biology



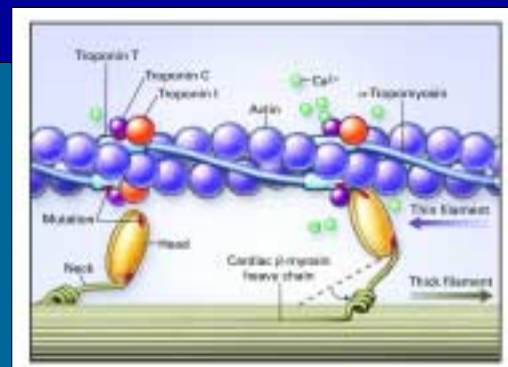
Molecular Cardiology

- Southern blot for DNA
- Northern blot for RNA
- Western blot for Proteins
- PCR - amplifies DNA and RNA
- Transgenic animals - study of a specific gene
- Micro array - study of gene expression

Presentation outline

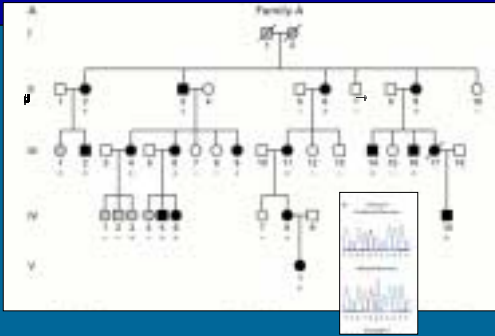
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From genes to proteins



Kamisago et al., NEJM 2000

cardiac-myosin heavy chain mutation is caused by a T to C transition at nucleotide 1680



Kamisago et al, NEJM 2000

Molecular defects linked to human CM

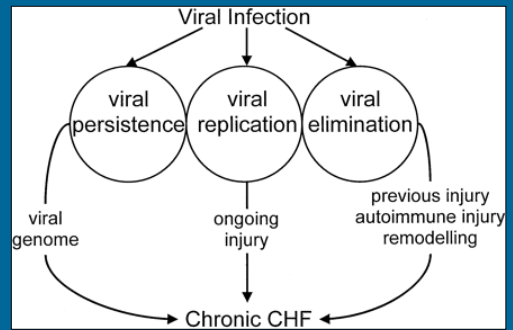
Table 1
Molecular defects linked to human cardiomyopathies

Genomic defects	Human defects		
	HCM	DCM	RCM
Sarcomere			
Myosin heavy chain	Missense (17-19)	Missense (20)	
Myosin essential light chain	Missense (21)		
Myosin regulatory light chain	Missense (21)		
Cardiac actin	Missense (22)		
Tropomyosin	Missense/deletion (19, 23)	Missense (3)	
Tropomyosin-T	Missense (7)	Deletion (20)	
α-Tropomyosin	Missense (19, 23)	Missense (24)	Missense (6)
Myosin binding protein-C	Missense/deletion (19, 25)		
Titin/titin-related protein			
Titin	Missense (26)	Missense/deletion (27, 28)	
Telethonin (T-cap)	Missense (14)		
Z-disk-associated proteins			
NLP	Missense (14)		
Sarcolemma cytoskeleton			
Dystrophin	Deletion (29-31)		
β-Sarcoglycan	Deletion/duplication (32)		
δ-Sarcoglycan	Missense (33)		
α-Dystrobrevin	Missense (34)		
Metavinculin	Deletion (35, 36)		
Intermediate filaments			
Desmin	Missense (37, 38)		
Lamin A/C	Missense (39)		

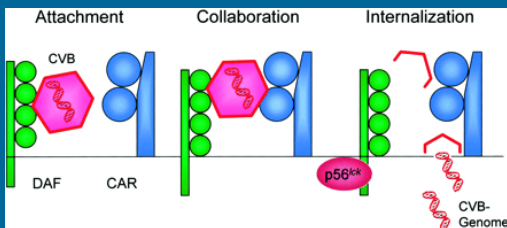
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Myocarditis

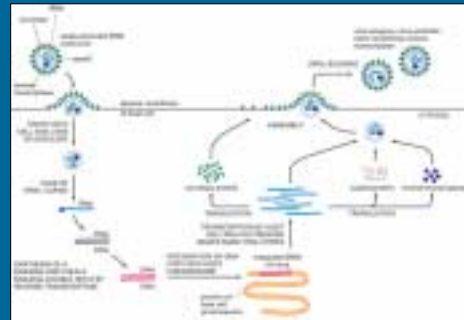


Viral entry to cells



Liu, PP, Mason JW. Circulation. 2001;104:1076-1082.

Viral Life Cycle



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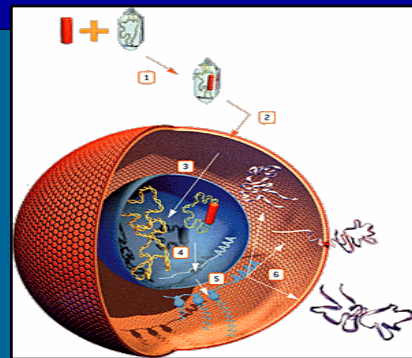
Molecular diagnosis

- Pharmacogenomics - Aspirin resistance
- Inherited syndromes - long QT, HCM
- Diagnostic MRI and molecular mapping - vulnerable plaques

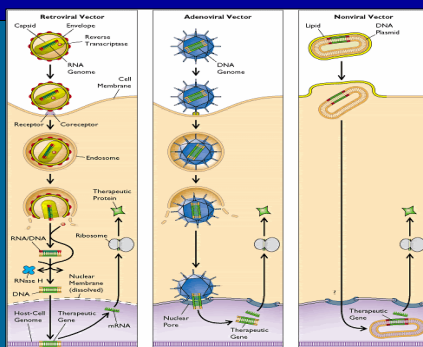
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Gene Transfer



Methods of Gene Transfer



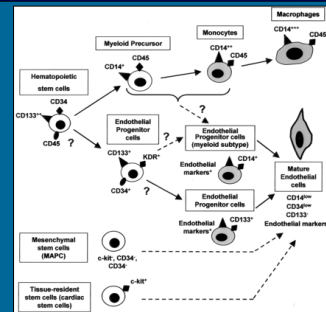
Therapeutics - Clinical

- Myogenesis by cell transfer
- Therapeutic angiogenesis by gene transfer:
 - FGF4
 - Del-1

Therapeutic - experimental

- Implantation of gene activated cells for angiogenesis, myogenesis, and EP
- Modification of myocytes phenotype by gene transfer:
 - Modifying EP
 - Modifying contraction

Angiogenesis & Myogenesis



Urbich & Dimmeler, Circ Res 2004

Angiogenesis & Myogenesis

Unresolved Questions: Angiogenesis

How to define an endothelial progenitor cell?
Origin of endothelial progenitor cells?
Definition of subpopulations with different functional capacities?
Signals for EPC homing and differentiation in vivo?
Optimization of ex vivo culture conditions to enhance the benefit of cell therapy?
Influence of the severity of vascular damage on the contribution of EPCs to regeneration?
Mechanisms of action?
Transdifferentiation capacity of different progenitor cells?
Importance of paracrine effects?

Urbich & Dimmeler, Circ Res 2004

Angiogenesis & Myogenesis

Unresolved Questions - Myogenesis

Which cells are involved?
BM or resident progenitors?
Definition of subpopulations with different functional capacities?
What is the mechanism?
Angiogenesis or myogenesis
Scar enhancement
Mechanisms of cell action?
Trans-differentiation or fusion?
Importance of paracrine effects?

Flugelman & Lewis, European Heart 2004

Recommended Literature

- Anversa P, Sussman MA, Bolli R. Molecular genetic advances in cardiovascular medicine: focus on the myocyte. *Circulation* 2004;109:2832-8.
- MacLellan WR, Lusis AJ. Dilated cardiomyopathy: learning to live with yourself. *Nat Med.* 2003;9:1455-6.
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- Schonbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors: statins as antiinflammatory agents? *Circulation.* 2004;109(21 Suppl 1):II18-26.
- Liu, PP, Mason JW. Advances in the understanding of myocarditis. *Circulation.* 2001;104:1076-1082.
- Melo LG, Pachori AS, Kong D, Gnecci M, Wang K, Pratt RE, and Dzau VJ. Molecular and Cell-Based Therapies for Protection, Rescue, and Repair of Ischemic Myocardium: Reasons for Cautious Optimism. *Circulation* 2004;109:2386 - 2393.