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Cardio-toxicity

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CARDIAC TOXIC RESPONSES

- The ultimate functional effect of cardiac toxic manifestations is

✓ decreased cardiac output

✓ and peripheral tissue hypoperfusion,

These effects is caused by alterations in

1. biochemical pathways
2. energy metabolism
3. cellular structural and function of the heart
4. electrophysiology
5. and contractility of the heart.

- These morphological and functional alterations induced by toxic exposure are referred to as toxicologic cardiomyopathy.
- The critical cellular event leading to toxicologic cardiomyopathy is:

✓ myocardial cell death

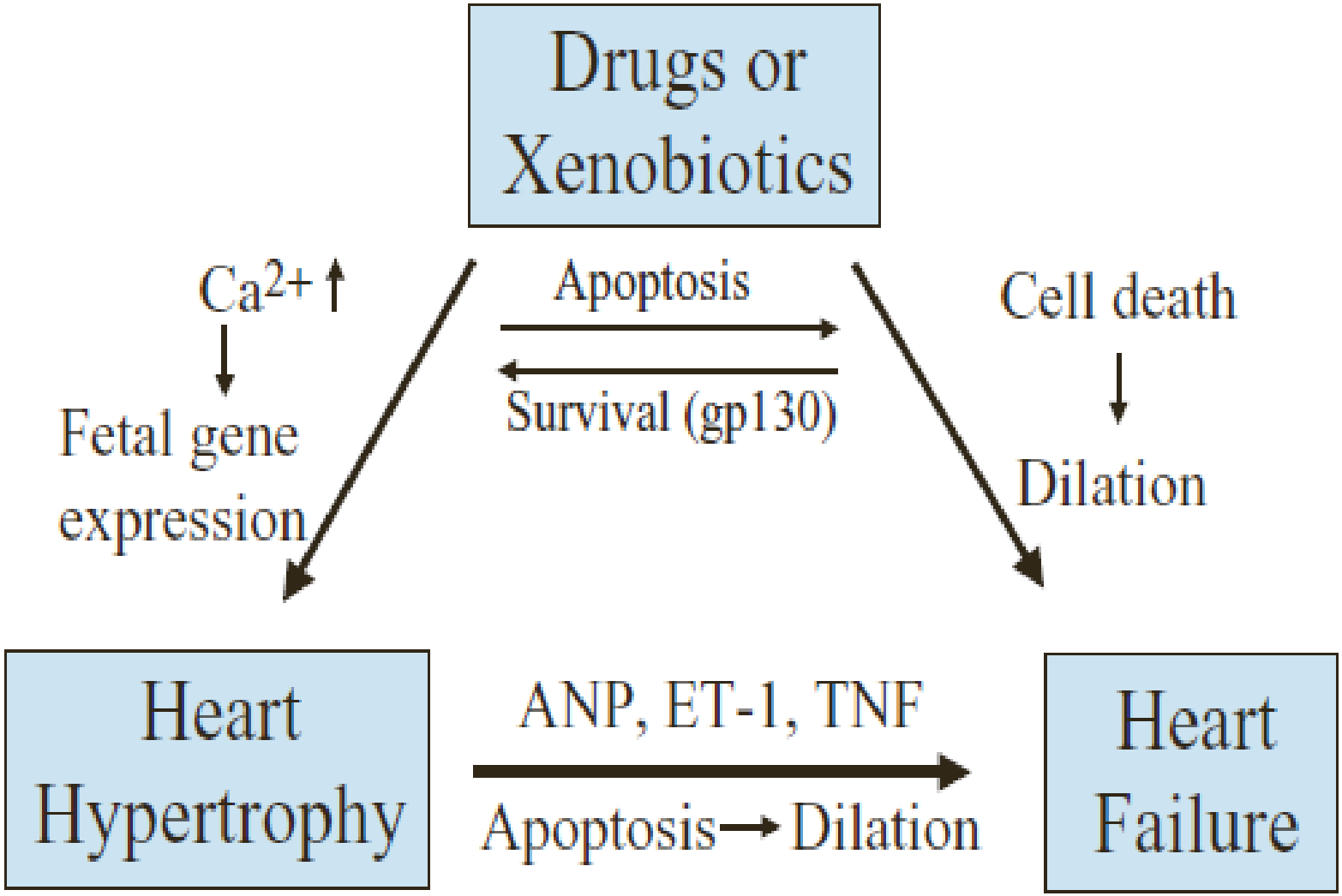
✓ and extracellular matrix remodeling.

- Manipulation of genes responsible for cardiac function can lead to a significant phenotype, often in the form of cardiac hypertrophy and heart failure.

- It is difficult to apply this knowledge to patients:

✓ Acquired cardiac disease such as heart failure is the result of interaction between environmental factors and genetic susceptibility.

✓ Extrinsic and intrinsic stresses produce lesions that cannot be explained by a single gene or a single pathway.


Drugs or Xenobiotics
Ca2+ ↑
Fetal gene expression
Apoptosis
Survival (gp130)
Cell death
Dilation
Heart Hypertrophy
ANP, ET-1, TNF
Apoptosis → Dilation
Heart Failure

Cardiac Arrhythmia

- Cardiac rhythms under physiological conditions are set by pacemaker cells that are normally capable of developing spontaneous depolarization and responsible for generating the cardiac rhythm, called automatic rhythm.

- A cardiac rhythm that deviates from the normal automatic rhythm is called cardiac arrhythmia, often manifested in the form of tachycardia.

- There are several classes of tachycardia, including sinus tachycardia, atrial tachycardia, ventricular tachycardia, and torsade de pointes (TdP).

- Subclasses such as atrial fibrillation, atrial flutter and accelerated idioventricular rhythm.

Cardiac Hypertrophy

- There are two basic forms of cardiac hypertrophy:
  - Concentric hypertrophy, which is often observed during pressure overload, and is characterized by new contractile-protein units assembled in parallel resulting in a relative increase in the width of individual cardiac myocytes.
  - Eccentric hypertrophy is characterized by the assembly of new contractile-protein units in series resulting in a relatively increase in the length of individual myocytes.

- Developing hypertrophy, during which period the cardiac workload exceeds cardiac output:

❑ compensatory hypertrophy, in which the workload/mass ratio is normalized and normal cardiac output is maintained;

❑ decompensatory hypertrophy, in which ventricular dilation develops and cardiac output progressively declines, and heart failure occurs.

Heart Failure

- A traditional definition of heart failure is the inability of the heart to maintain cardiac output sufficient to meet the metabolic and oxygen demands of peripheral tissues.

- Definition has been modified recently to include changes in systolic and diastolic function that reflect specific alterations in ventricular function and abnormalities in a variety of subcellular processes.

- A detailed analysis to distinguish right ventricular from left ventricular failure can provide a better understanding of the nature of the heart failure and predicting the prognosis.

Acute and Chronic Cardiac Toxicity

- **Acute cardiac toxicity:**

✓ cardiac response to a single exposure to a high dose of cardiac toxic chemicals.

✓ Is often manifested by cardiac arrhythmia.

✓ Myocardial apoptosis is also involved.

Examples:

❖ A single high dose of arsenic can lead to cardiac arrhythmia and sudden cardiac death, which is easy to measure.

❖ A single dose of monensin leads to a diminished cardiac function progressing to heart failure requires a long-term observation (a few months) which is difficult to measure.

- **Chronic cardiac toxicity:**

✓ Response to long-term exposure to chemicals, manifested by cardiac hypertrophy and the transition to heart failure.