Structural analysis of SUMO-interacting motif-2 on PIAS protein with acetylated SUMO in the context of coronary heart disease

Hemsai Yadav and Ravikiran S. Yedidi*

The Center for Advanced-Applied Biological Sciences & Entrepreneurship (TCABS-E), Visakhapatnam, Andhra Pradesh, India. 530002.

*Correspondence to RSY: tcabse.india@gmail.com

INTRODUCTION

Coronary artery disease is the most common type of heart disease. It is also the leading cause of death for both men and women in the world. It occurs when fatty deposits called plaque build up inside the coronary arteries. The coronary arteries wrap around the heart and supply it with blood and oxygen. When plaque builds up, it narrows the arteries and reduces the amount of blood that gets to your heart.it is the most common type of heart disease, killing 365,914 people in 2017. About 18.2 million adults age 20 and older have CAD (about 6.7%). About 2 in 10 deaths from CAD happen in adults less than 65 years old. Cardiovascular diseases, especially coronary heart disease (CHD), are epidemic in India. The Registrar General of India reported that CHD led to 17% of total deaths and 26% of adult deaths in 2001-2003, which increased to 23% of total and 32% of adult deaths in 2010-2013. (Fig-3)

RISK FACTORS:
MODIFIABLE RISK FACTORS:
Tobacco use High blood cholesterol or triglyceride levels Lack of exercise Obesity Stress.

NONMODIFIABLE RISK FACTORS:
Family history of heart disease Older age Diabetes High blood pressure.

Causes
Development of atherosclerosis (Fig-2) ; Coronary artery disease is thought to begin with damage or injury to the inner layer of a coronary artery, sometimes as early as childhood. The damage may be caused by various factors, including: Smoking, High blood pressure,High cholesterol,Diabetes or insulin resistance Sedentary lifestyle.

SYMPTOMS: CARDIOVASCULAR -
1 .Angina pectoris, 2.Ischemia, 3.Low cardiac output 4.Bradycardia (Decrease pulse rate) , 5.Hypertension ,6.Myocardial infarction, 7.Diaphoresis-excessive sweating ,8.ECG changes – ST segment and T wave changes, also show tachycardia, bradycardia, or dysrhythmias.

RESPIRATORY- Dyspnea-Shortness of breath, Pulmonary edema ,Chest heaviness, Fatigue
Genitourinary- Decreased Urinary Output May Indicate Cardiogenic Shock.
Gastrointestinal- Nausea And Vomiting
Skin- Cool, Clammy ,Diaphoretic , And Pale Appearance On Skin.
complications :
chest pain (angina) heart attack , heart failure and abnormal heart rhythm (arrhythmia).
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PREVENTION:
1.Quit smoking 2.Control conditions such as high blood pressure 3. high cholesterol and diabetes 4. Stay physically active 5. Eat a low-fat, low-salt diet that's rich in fruits, vegetables and whole grains 6. Maintain a healthy weight 7,Reduce and manage stress

MEDICAL MANAGEMENT: Various drugs can be used to treat coronary artery disease, including: Vasodilators (These drugs acts as blood vessel dilator): Nitrates Beta-Blockers (Decrease workload in heart): Propranolol 20-40 mg Calcium channel blocker (They improve coronary blood flow): • Nifedipine • Verapamil
Anticoagulant Drugs: Heparin , Opiate Analgesic (For reduce pain), Morphine sulphate ,Thrombolytic Drugs: , Streptokinase,Urokinase
ANTIHYPERTENSIVE MEDICINES- Methyldopa- This medication is used alone or with other medications to treat high blood pressure (hypertension). Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Methyldopa works by relaxing blood vessels so blood can flow more easily. Sodium nitroprusside- It is used for lowering the blood pressure. Amlodipine- Amlodipine is used with or without other medications to treat high blood pressure. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Dose-10 mg,20 mg.
SURGICAL MANAGEMENT: Angioplasty and stent placement (percutaneous coronary revascularization): Coronary artery bypass surgery.

EXPERIMENTALS

The analysis includes
evaluation of the secondary structure alpha-helices and beta-strands by using pymol software. **(FIG-1)**

Number of results: (20504)
Filters: Homosapiens.
The results are filtered by choosing the required species. The selected species here is Homosapiens.
Number of results: (11946)
Number of structures obtained after selecting Homosapiens is 11946.
Experimental method:
X-ray diffraction: 18146 results are obtained
Electron microscopy: 932 results are obtained
Solution NMR: 1372 results are obtained
The above results are taken into consideration and X-ray diffraction method is selected (18146)
Refinement resolution: (5754)
Refinement resolution is selected in the range from 1.5 to 2.0 and the results obtained are 5754
PDB ID: 6V7R
Title: Crystal structure of K37 – acetylated SUMO1 in complex with PIAS- SIM2.
Experimental Data snapshot:
Method: X-ray diffraction
Resolution: 1.55 Å
R-value Free: 0.221 (22.1%)
R-value work: 0.182(18.2%)
Tests required to confirm the structure quality:
1. R-work value should be roughly equal to one tenth of resolution value: R-work value =0.182 (18.4%)
One tenth of resolution is 1.55/10 = 0.155 (15.5%)
Statement: R-work is greater than 1/10 of the resolution.
R-work value is not equal to 1/10th of the resolution.
∴ Fail

2. The difference between the R-free and R-work values should be less than or equal to 0.05(5%)
R-free - R-work
= 0.221 - 0.182
= 0.039 (3.9%)

Statement: The difference between R-free and R-work is less than 0.05(5%).
∴ Pass
 Macromolecule:
Entity id: 1
Small ubiquitin-related modifier 1

Entity id: 2
Protein PIAS

Small molecule: (ligand)
Entity id: 1
Ligand id: ALY

Crystal structure of K37-acetylated SUMO1 in complex with PIAS-SIM2
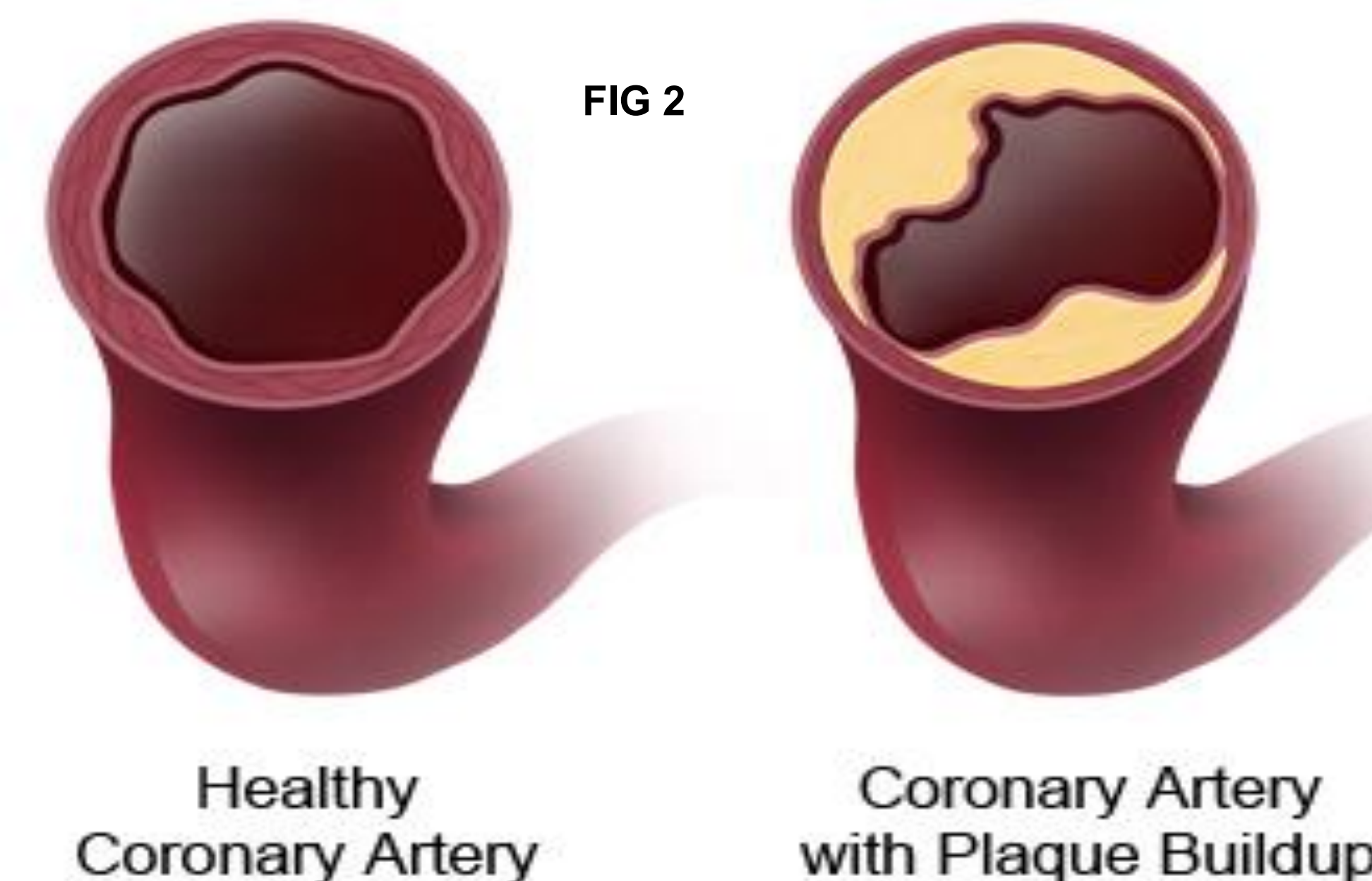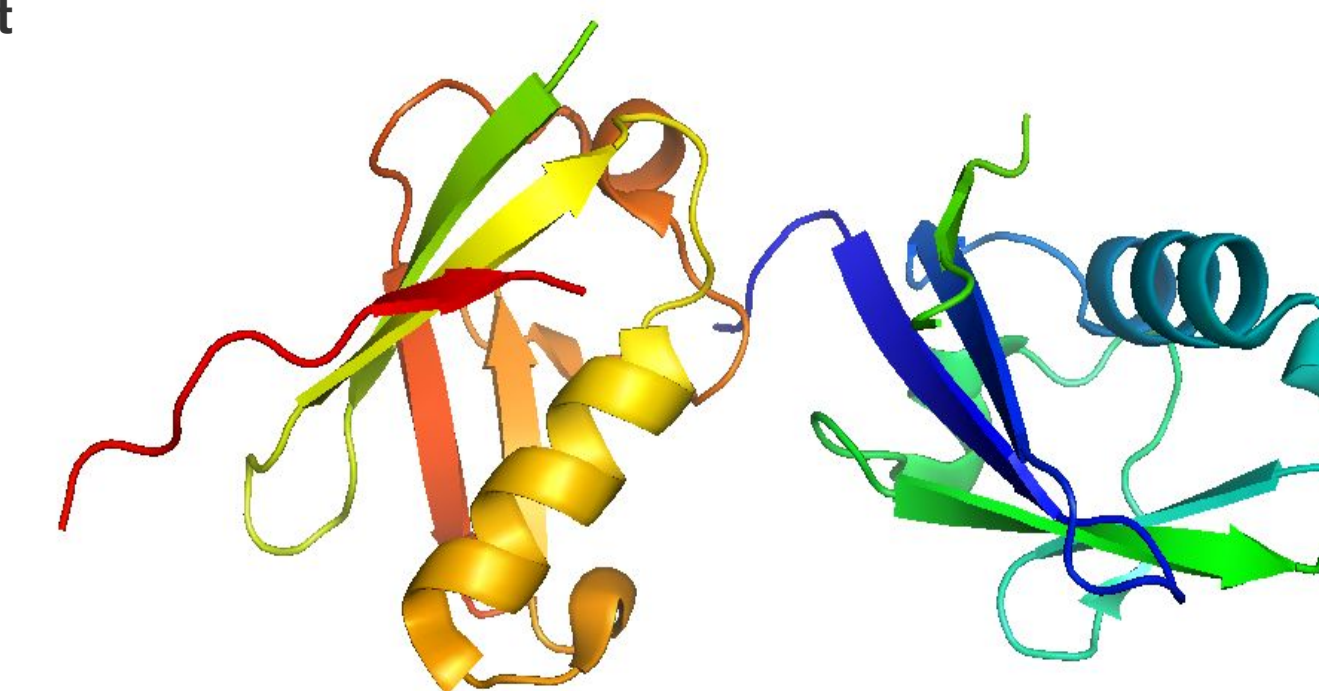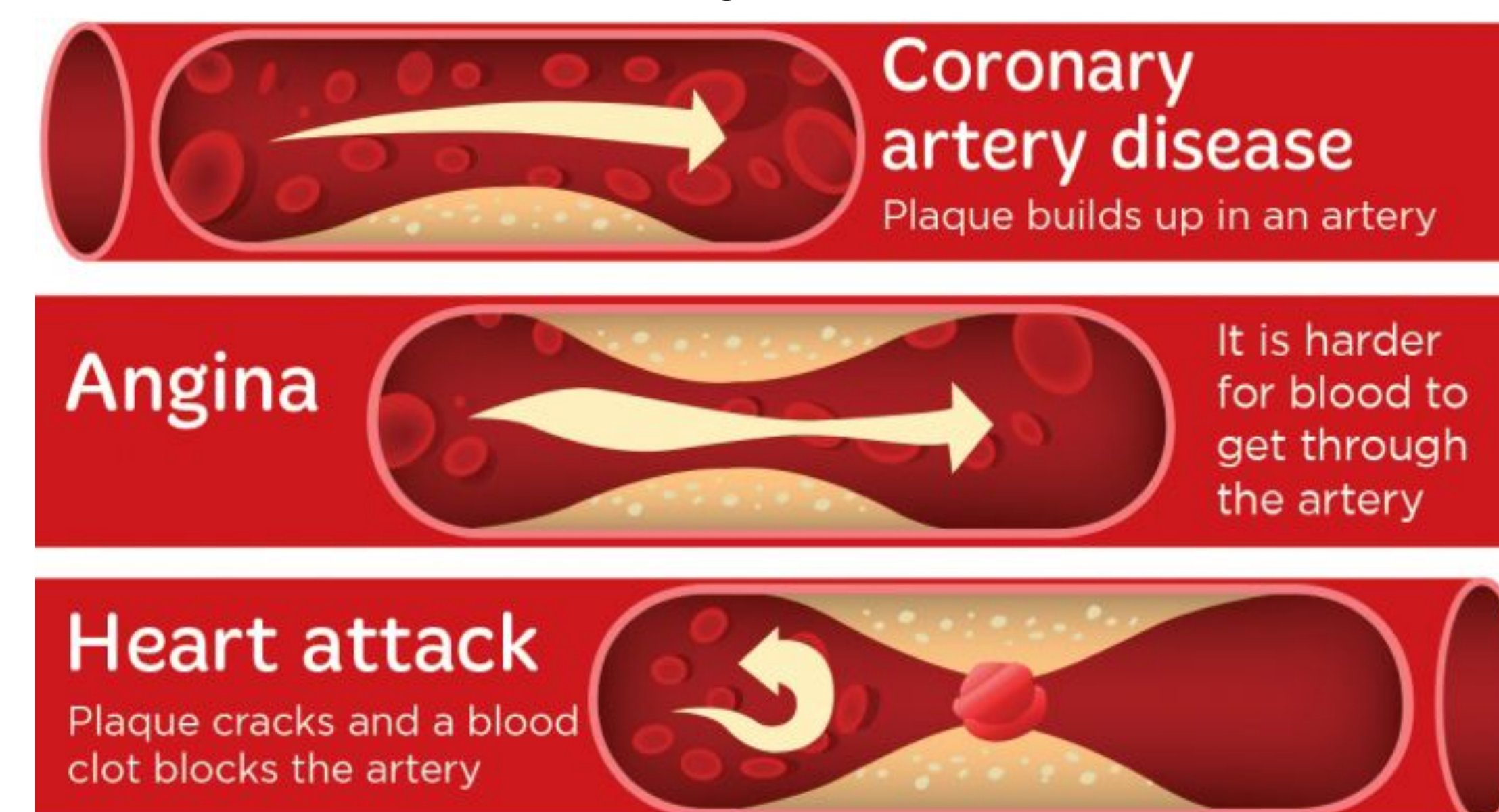FIG-1

FIG 2

Healthy Coronary Artery

Coronary Artery with Plaque Buildup

Fig-3

Coronary artery disease
Plaque builds up in an artery

Angina
It is harder for blood to get through the artery

Heart attack
Plaque cracks and a blood clot blocks the artery

RESULTS & DISCUSSION

The human PIAS proteins are small ubiquitin-like modifier (SUMO) E3 ligases that participate in important cellular functions. Several of these functions depend on a conserved SUMO-interacting motif (SIM) located in the central region of all PIAS proteins (SIM1). Recently, it was determined that Siz2, a yeast homolog of PIAS proteins, possesses a second SIM at its C terminus (SIM2). Sequence alignment indicates that a SIM2 is also present in PIAS1-3, but not PIAS4. Using biochemical and structural studies, we demonstrate PIAS-SIM2 binds to SUMO1, but that phosphorylation of the PIAS-SIM2 or acetylation of SUMO1 alter this interaction in a manner distinct from what is observed for the PIAS-SIM1. We also show that the PIAS-SIM2 plays a key role in formation of a UBC9-PIAS1-SUMO1 complex. These results provide insights into how post-translational modifications selectively regulate the specificity of multiple SIMs found in the PIAS proteins by exploiting the plasticity built into the SUMO-SIM binding interface.

the structure of PIAS SIM2 PDBI id (6V7R) consists of six alpha helices and twelve beta strands.

REFERENCES

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