SMART Teams 2015-2016
Research and Design Phase

Marquette University High School SMART Team

P Ahn, K Arnhold, N Cowan, N Dittrich, R Foster, J Gorski, R Johnson, H Khalil, C Kim, M Malone, S Mohiuddin, L Ortega, J Otten, M Rivera, M Rose, P Rozewicz, A Sabatino, T Sargent, J Smith, D Strom, J Strom, B Tsuji, J Yamat, N Yorke

Advisor: Carl Kaiser & Keith Klestinski

Mentor: Judy Maloney, Ph.D.
Marquette University, Department of BioMedical Sciences

Effect of Inhibiting NFκB on Ischemia-Reperfusion-Induced Cell Apoptosis, Necrosis in Cardiac Myocytes

PDB: 1VKX

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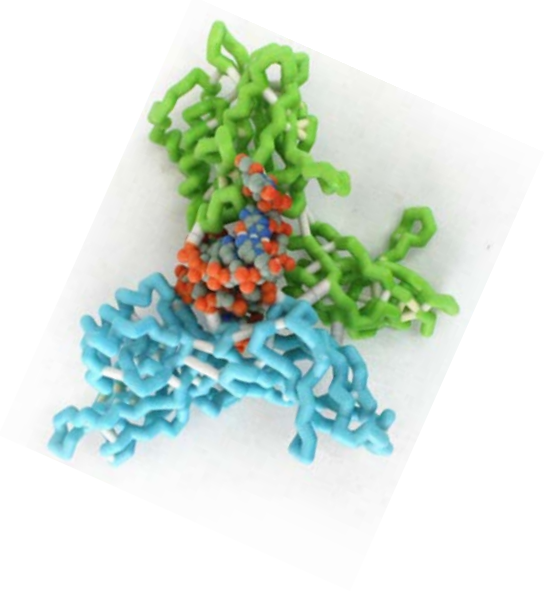

Format: Alpha carbon backbone

RP: Zcorp with plaster

Description:

Cardiovascular disease and its complications are the leading cause of morbidity and mortality in the United States. A myocardial infarction (MI) is caused by a blood clot in a coronary artery and results in loss of blood flow to the heart (ischemia). To prevent necrosis or cell death of heart tissue, ischemia is treated with reperfusion therapy, in which blood flow is restored. Reperfusion therapy paradoxically causes damage to the heart muscle cells via the activation of Nuclear Factor Kappa Beta (NFκB) which can trigger apoptosis or programed cell death, or via the generation of reactive oxygen species and subsequently further necrosis. The extent to which the transcription factor NFκB promotes cell death or even promotes survival is unknown. However, it is known to be a key inflammatory mediator that coordinates cell homeostasis under bodily stress, as with an MI or ischemia reperfusion (IR) injury. NFκB is complexed with Inhibitor Kappa Beta (IκB) and exists as a larger IκB/NFκB complex within the cytosol of the cell until inflammatory mediators activate an IκB kinase. Phosphorylation of this larger complex separates IκB from NFκB, at which point NFκB translocates to the nucleus of the cell, binds to DNA, and initiates transcription of genes responsible for apoptosis. The Marquette University High School SMART (Students Modeling A Research Topic) Team modeled NFκB, a heterodimer, which, in the heart, is composed of the subunits, p50 and p65, complexed with DNA. To study the effect of NFκB inhibition on IR-induced apoptosis and necrosis, cultured cardiac myocytes received two hours of ischemia, and were reperfused with or without the NFκB inhibitor, N4-[2-(4-phenoxyphenyl)ethyl]-4,6-quinazolinediamine (QNZ). Caspase 3 activation and annexin V staining, measurements of apoptosis, revealed that inhibiting NF-κB caused a decrease in IR-induced apoptosis. Propidium iodide staining, a measurement of cell necrosis, revealed that inhibiting NF-κB caused an increase in IR-induced necrosis. Further studies into understanding the effect of NFκB inhibition on IR injury may help provide novel therapies.

Specific Model Information:

Protein backbone displayed with the DNA displayed in spacefill.
NF-KAPPA-B P65 subunit: colored cyan
NF-KAPPA-B P50D subunit: colored chartreuse
DNA: colored CPK
HBonds: colored papayawhip
Struts: colored white
G of consensus sequence: colored purple
C of consensus sequence: colored magenta

http://cbm.msoe.edu/smartTeams/index.php

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