# A NOVEL SYSTEMS BIOLOGY & BIOINFORMATICS APPROACH FOR IDENTIFYING EVOLUTIONARY TRADE-OFFS
(ATHEROGENESIS & ATHEROSCLEROSIS)

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R&D SYSTEMS a biotechne brand — Atherosclerosis Disease Progression

BACKGROUND

Vulnerability to atherosclerosis represents an evolutionary trade-off: balancing the liability associated with the pathology against the multiple biological benefits contained within the phenotype of vulnerability. Emerging bioinformatic platforms enable a pathway-level analysis of these evolutionary trade-offs. Here we present a novel systems biology approach using publicly available gene expression pathway platforms to depict the series of overlapping and interdependent physiological and pathophysiological processes which play central roles in both atherogenesis and critical physiologic functions.
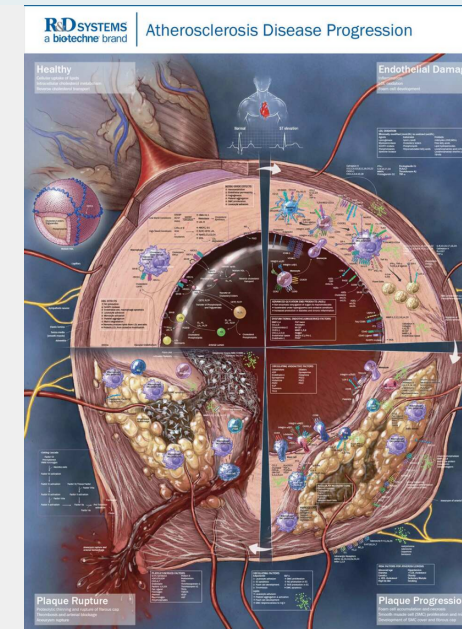
OBJECTIVES

We aimed to develop a method for identifying overlapping pathophysiological and physiological gene expression pathways for human disease. A criterion for our methodology was to make use of publicly available gene expression pathway platforms exclusively. With our results, we sought to create visualization techniques illustrating and emphasizing the evolutionary tradeoffs for human diseases. For demonstrating our methodology, we used the leading cause of death in our species, atherosclerosis.

METHODOLOGY

a) To identify the overlap between pathophysiological atherogenic pathways and physiological (biologically beneficial) pathways:

1 . We utilized KEGG (Kyoto Encyclopedia of Genes and Genomes) to source genes that are key to several canonic atherosclerosis pathways.

2 . Each gene from the pathway was compiled (215 total).

3 . We imported the compiled genes into Gene Analytics.
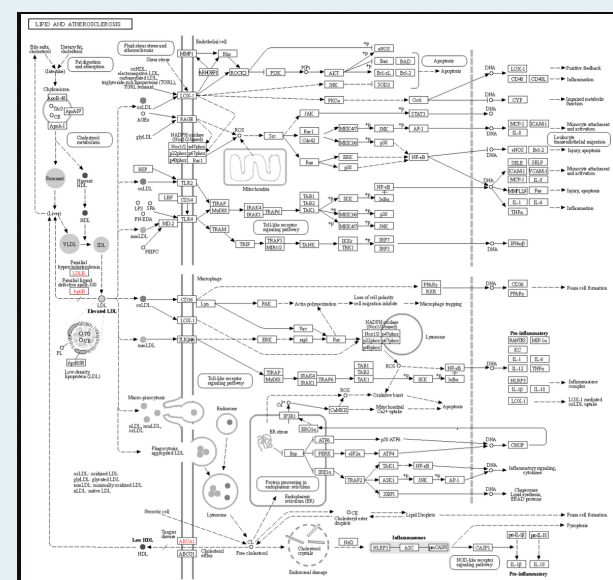
ABCA1, ABCG1, AGER, AKT1, AKT2, AKT3, APAF1, APOA1, APOA4, APOB, ARHGEF1, ATF4, ATF6, BAD, BAX, BCL2, BCL2L1, BID, CALM1, CALM2, CALM3, CALML3, CALML4, CALML5, CALML6, CAMK2A, CAMK2B, CAMK2D, CAMK2G, CASP1, CASP3, CASP6, CASP7, CASP8, CASP9, CCL2, CCL3, CCL3L1, CCL3L3, CCL5, CD14, CD36, CD40, CD40LG, CDC42, CHUK, CXCL1, CXCL2, CXCL3, CXCL8, CYBA, CYBB, CYCS, CYP1A1, CYP2A6, CYP2A7, CYP2B6, CYP2C8, CYP2C9, CYP2J2, DDIT3, EIF2AK3, EIF2S1, ERN1, ERO1A, FAS, FASLG, FOS, GSK3B, HRAS, HSP90AA1, HSP90AB1, HSP90B1, HSPA1A, HSPA1B, HSPA1L, HSPA2, HSPA4, HSPA5, HSPA6, HSPA8, HSPD1, ICAM1, IFNA1, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA2, IFNA21, IFNA4, IFNA5, IFNA6, IFNA7, IFNA8, IFNB1, IKBKB, IKBKE, IKBKG, IL12A, IL12B, IL1B, IL1B, IL6, IRAK1, IRAK4, IRF3, IRF7, ITPR1, JAK2, JUN, KRAS, LBP, LDLR, LY96, LYN, MAP2K3, MAP2K4, MAP2K6, MAP2K7, MAP3K5, MAP3K7, MAPK1, MAPK10, MAPK11, MAPK12, MAPK13, MAPK14, MAPK3, MAPK8, MAPK9, MIB1, MIB2, MMP1, MMP3, MMP9, MYD88, NCF1, NCF2, NCF4, NFATC1, NFATC2, NFATC3, NFE2L2, NFKB1, NFKBIA, NLRP3, NOS3, NOX1, NRAS, OLR1, PDPK1, PIK3CA, PIK3CB, PIK3CD, PIK3R1, PIK3R2, PIK3R3, PLCB1, PLCB2, PLCB3, PLCB4, PLCG1, POU2F1, POU2F2, POU2F3, PPARG, PPP3CA, PPP3CB, PPP3CC, PPP3R1, PPP3R2, PRKCA, PTK2, PYCARD, RAC1, RAP1A, RAP1B, RELA, RHOA, ROCK2, RXRA, RXRB, RXRG, SELE, SELP, SOD2, SRC, STAT3, TAB1, TAB2, TANK, TBK1, TICAM1, TICAM2, TIRAP, TLR2, TLR4, TLR6, TNF, TNFRSF10A, TNFRSF10B, TNFRSF1A, TNFSF10, TP53, TRAF2, TRAF3, TRAF6, VAV1, VAV2, VAV3, VCAM1, VLDLR, XBP1

GENE ANALYTICS RESULT FOR: ATHEROSCLEROSIS PATHWAYS
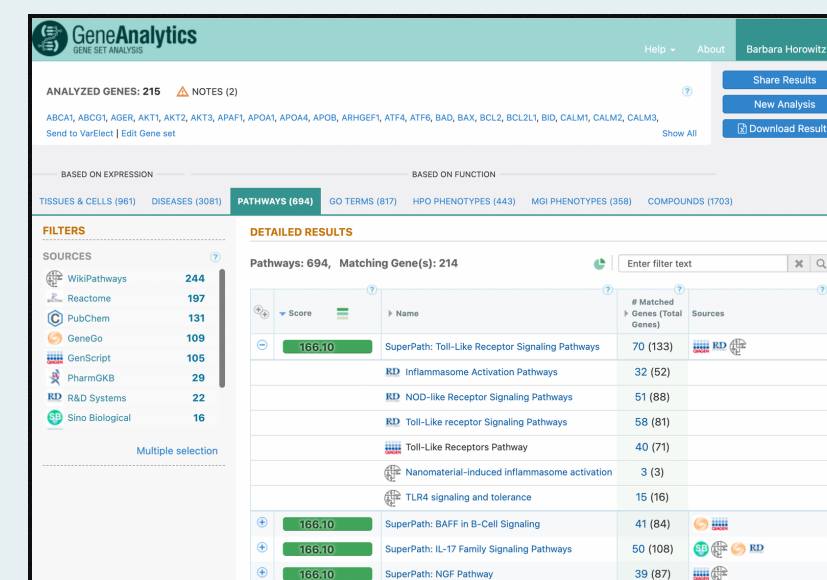
Gene Analytics provides a ranked list of physiological (biologically beneficial) pathways that overlap with the pathophysiological atherogenic pathways.

The top 3 physiological (biologically beneficial) pathways that maximally overlap with the pathophysiologic atherogenic pathways are the:

1. **Immune Caspase-1 Activation Pathways**
2. **NOD-like Receptor Pathways**
3. **Toll-like Receptor Signaling Pathways**

Note: the top 3 physiologic pathways that overlap with pathophysiologic atherogenic pathways are heavily linked to immune physiology

b) To visualize the degree of overlap between pathophysiological atherogenic pathways and the top 3 physiological pathways:

1 . We compared the gene sequences found in the pathophysiological atherogenic pathways with those found in the physiological pathways.

2 . We then superimposed the overlapping physiological and pathophysiological pathways. For example:

ATHEROSCLEROSIS PATHWAY

TOLL-LIKE RECEPTOR SIGNALING PATHWAY

+

We replicated sections in the RnD Systems pathway from the GeneAnalytics result to enable overlap visualization

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TOLL-LIKE RECEPTOR SIGNALING PATHWAY
SUPERIMPOSED ONTO THE ATHEROSCLEROSIS PATHWAY

LEGEND
Yellow Box: Pathophysiology
Blue Box: Physiology
Turquoise Circles: Overlapping Genes
Turquoise Arrows: Convergent Pathways

QR CODE TO ANIMATED DECK

IMPLICATIONS & CONCLUSION

The proximate causes of atherosclerosis have been extensively studied and characterized since the Framingham Heart Study. While classic atherosclerosis risk factors, such as cholesterol, hypertension, and lifestyle (diet and sedentary behavior), play a significant role in determining susceptibility to atherosclerosis, our study focuses on exploring the often-overlooked vulnerability to atherogenesis from an evolutionary perspective. We present a methodology for exploring non-proximate (evolutionary) processes shaping vulnerability to atherosclerosis.

We developed a user-friendly methodology that could be easily used by physicians and medical students for identifying overlapping pathophysiologic and physiologic gene expression pathways, applicable to various human diseases. Our approach emphasizes clarity of visual depiction of these overlaps to drive home the following central concept in evolutionary medicine: **Embedded within the biology of vulnerability to disease, are dense networks of interdependent and overlapping biologically beneficial pathways. These components of vulnerability have evolved over an evolutionary timescale.** Recognizing their biological benefits enhances our understanding of evolutionary tradeoffs. Strengthening our knowledge of their functions and influence promises more informed development of strategies for treatment and prevention. Our method for identifying and visualizing these components of vulnerability offers a novel method for clarifying the nature of evolutionary tradeoffs underlying vulnerability to human pathology.
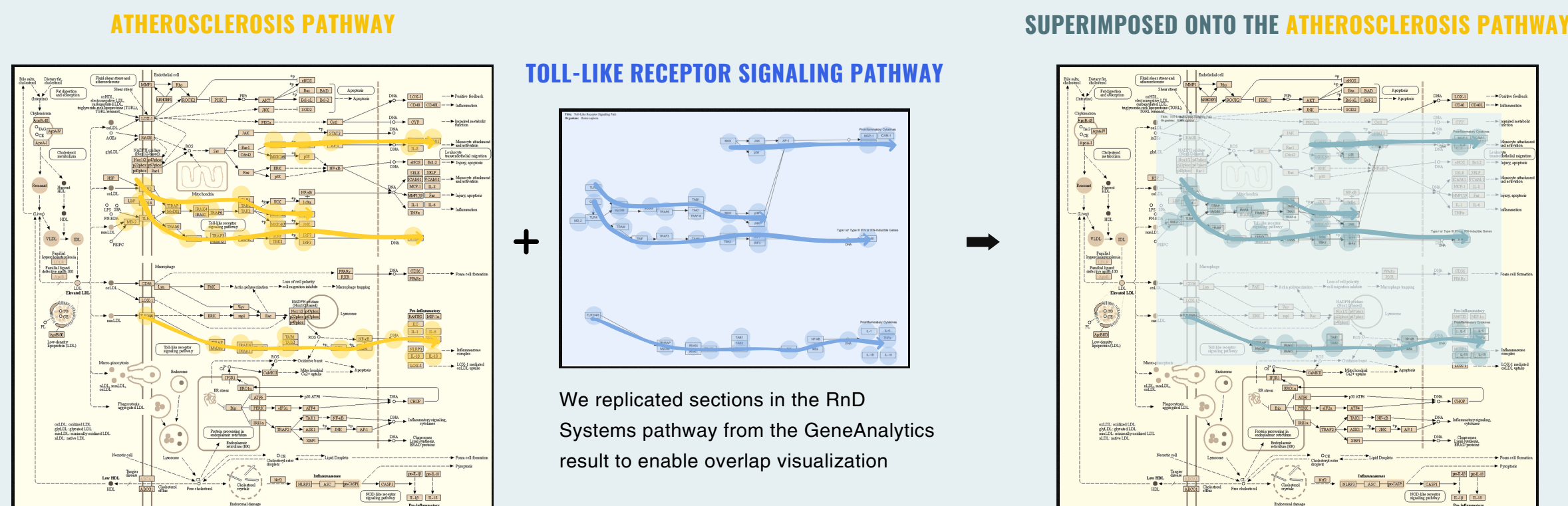
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