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EDITORIAL

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Solving the "Heart Attack" Puzzle

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Ischemic heart disease is a leading cause of death today, and is believed to have existed as early as the early stage of human civilization when the development of agriculture allowed rich food. The earliest scientific evidence of ischemic heart disease includes the description of the coronary circulation by Harvey (1649), identification of angina pectoris by Heberden (1772), "myomalacia cordis" by Ziegler (1880), and reviews of autopsy cases of myocardial infarction by Mallory (1939). Today, as research technology advances, the number of research studies regarding ischemic heart disease is rising exponentially. Very well, but are we really getting any closer to solving this one of the biggest human issues?

A Pubmed search using the keyword "ischemic heart disease" returns 24,681 hits as of April 26, 2019 (removing quotation marks increases the hits to 484,723). Limiting the above search to review articles, the number of hits is 4,194 (63,496 without quotation marks). It makes sense considering so many mechanisms are involved in this tough problem. Examples include but not limited to oxidative stress, calcium transport, vasoconstriction, complement activation, inflammation, apoptosis, necrosis, autophagy, protease activation, and protein SUMOylation. Pathways related to cardioprotective signaling during ischemia reperfusion include Phospholipase D signaling, Akt signaling, AMP-activated protein kinase (AMPK), activated protein C (APC), HIF hydroxylase, cyclooxygenase-1/mPGES-1/endothelial prostaglandin EP4 receptor, TLR4/MyD88/NF-κB/NLRP3 inflammasome, and autophagy-lysosome. When it comes to individual pharmacological reagents or targets identified, the list is endless! New targets are being found one after another, and the rate of discovery is even getting faster.

What is astounding is that the inhibition or activation of a specific target is often reported to have dramatic protective effect against cardiac ischemic disease (usually using cellular and/or animal model), and these likely-promising targets are being found one after another. Indeed, due to a lack of time and resources, research teams will often focus on a single target or pathway. Another thing is that we love a simple story. The idea of a simple, single mechanism or target pathway is very appealing. The problem is, the pieces of the puzzle are increasing in number, but remain disconnected from one another. We still can't see the whole picture yet.

A big problem, often or always, has multiple factors, which are intertwined together. Pieces should be connected to complete a puzzle. That said, who the hell can put them all together, where just recognizing a piece (reading an article) takes tens of minutes, and there are tens or even hundreds of thousands of them? And hell yes, they are still increasing—exponentially. As the puzzle is demoralizingly huge, it may be the artificial intelligence that will complete it. Be that as it may, it is always important to imagine the whole picture.

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