A New Approach to an Old Problem
One Brave Idea

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Despite sophisticated and increasingly effective assaults on traditional atherosclerotic risk factors, in particular LDL (low-density lipoprotein cholesterol) and most recently inflammation, there remains a large, unmet coronary heart disease (CHD) burden.[1] Modern experimental and therapeutic programs have focused on a small number of biological pathways, so it is possible that we have reached the point where to identify additional causal mechanisms and create novel therapies, fundamentally new approaches are required. The recently developed One Brave Idea program, generously sponsored by the American Heart Association and Verily with AstraZeneca, was designed to identify alternative strategies to address CHD. In this perspective, we examine the existing frameworks in atherosclerosis biology, highlighting their successes and focusing on areas where there may be missing information. We will outline general principles which would enable biomedical researchers to identify and capture relevant missing information in CHD. Central to the program are efforts to radically improve the phenotypic repertoire of human biology and to define environmental drivers of disease, including nutrition, at a resolution and scale only feasible in the current connected era. This approach also implies the potential for a universal objective framework for the definition of personal health or disease, harmonized across the entire biomedical community to accelerate the integration of discovery more fully with prevention and clinical care.

Current Study of Coronary Disease in Man

To find disease causation, one must first detect exposures (environmental or genetic) of large enough effect size that they can be clearly associated with specific outcomes. Many associations may be observed, but only a small number of such correlations are truly causal or represent targets for therapeutic intervention. Defining causality or therapeutic efficacy is demanding, particularly when observations are sparse and temporally distant from the outcomes of relevance. By measuring both exposures and outcomes at a more granular level and across time, causality is more readily inferred.

Current measurement of exposures is so limited that it is not surprising that no new environmental contributors to CHD have been identified in decades. The inherited contribution to CHD has been examined through various genetic techniques, implicating large numbers of loci, a few of large effect (mainly through family studies), and the majority of modest effect (through genome-wide association studies).[2] Small-effect size loci, while they may represent signals from larger effects operant in discrete subsets of CHD, or indeed be relevant drug targets, are individually insufficient to cause the disease phenotype across a population, rendering the process of mechanistic testing challenging.

The lipid hypothesis, that elevated LDL causes CHD, may be held up as an example of completing the case for causality.[3] Classical large epidemiology studies linked serum cholesterol with incidence of CHD at the population level.[4] Corroborating mutations in the gene encoding the LDLR (LDL receptor) were shown to be causal in some forms of familial CHD, and subsequently associations have also been observed in common variant studies.[2,3] Finally, confirmation of the centrality of this mechanism has come from trials showing that agents which indirectly increase the availability of LDLR also reduce vascular events.[5,6]

Missing Causal Mechanisms in CHD

Despite these remarkable achievements, there is evidence that not only are there significant uncharted mechanisms driving CHD but also that well-understood risk factors may act through additional, unappreciated intermediaries. The scientific process by its nature consistently reinforces canonical mechanisms and so erodes our opportunity for the detection of novel pathways.

Genetic contributions to the risk of CHD are considerable. Twin studies estimate heritability at over 50% with monozygotic to dizygotic risk ratios in those under the age of 55, suggesting Mendelian inheritance patterns in these age groups.[7] Since the advent of genome-wide association studies, >100 common variants have been associated with CHD, cumulatively explaining ≈30% to 40% of CHD heritability.[2] Because most common variants lie outside structural coding regions, the ascribed mechanism is often based on the nearest gene that conforms to recognized atherogenic pathways (lipid metabolism, inflammatory signaling, cellular proliferation, etc.). Even with this generous attribution scheme, 50% of the known loci have no pathway annotations, highlighting the mechanistic gap between genetic variation and disease.

The challenges moving from association to biological mechanism cannot be underestimated.[8] For example, the exact mechanisms of variants at the 9p21 or 1p13 loci, consistently

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identified since the earliest genome-wide association studies for CHD, remain largely unclear despite intense research.[9] Variation at the 1p13 locus is strongly associated with raised LDL and increased risk of myocardial infarction, and elegant experimentation has yielded a potential mechanistic link to the observed raised CHD risk via altered function of a hepatic transcription factor and one of its regulated genes, SORT1 (sortilin 1).[10] Despite strong association with serum cholesterol, the increased myocardial infarction risk for a homozygote is discordant, suggesting additional contributory mechanisms.

Monogenic forms of CHD represent the known causal pathways, though even in these settings there are also clues that traditional mechanistic paradigms leave aspects of the biology unexplained. Thus, in familial hypercholesterolemia (FH), mutant carriers have significantly higher CHD risk when compared with their LDL-matched non-FH counterparts. Some excess risk might be accounted for by lifelong cholesterol exposure, but much of the hypercholesterolemia in non-FH patients also has a genetic basis, albeit polygenic, and is associated with similar cumulative exposure. In a recent study, 27% of FH patients were normocholesterolemic, and among those with normal LDL levels, subjects with FH mutations are still twice as likely to have CHD as non-FH patients.[11] The dissociation between CHD risk and LDL in FH is also seen earlier in life. In FH children, carotid intima-media thickness, a metric that correlates with traditional risk factors and cardiovascular outcomes in unselected populations, was predicted strongly by male sex and age, but only weakly by LDL level.[12]

One example of a more agnostic view of monogenic atherosclerotic disorders is that they share abnormal lipoprotein-dependent signals in the Wnt pathway, beyond simple effects on LDL transport. Reflecting this, FH patients have lower rates of cancer and type 2 diabetes mellitus, and conversely, statins, which indirectly increase LDLR levels, are associated with increased incidence of type 2 diabetes mellitus.[13,14] Nontraditional atherosclerotic mechanisms are further emphasized by the discovery of a Mendelian syndrome of premature CHD, osteoporosis, and metabolic abnormality because of mutations in the LDLR-related protein 6 (LRP6) gene, a member of the LDLR gene family that acts as a coreceptor for Wnt ligands.[15] A common LRP6 variant, first identified as an Alzheimer risk locus, also impairs canonical Wnt signaling and is strongly associated with atherosclerotic and bone phenotypes.[15]

Supporting data also emerge from drug trials. Although several LDL-reducing agents also reduce CHD event risk and increase survival proportionately, there are other interventions where dissociation between LDL-lowering and improved clinical outcomes becomes apparent. Disentangling the LDL-independent benefits of statins is challenging because additional effects mediated through isoprenoid pathways also correlate with LDL levels. There is also evidence that pleiotropic effects may be of importance in the net beneficial outcomes observed with statins, but not seen with other LDL-lowering interventions. Similarly, although PCKS9 inhibitors lower LDL very effectively, their net effects may also include other pathways dependent on proprotein convertase function.

New Approach

The persistence of CHD as the leading cause of mortality combined with evidence of unknown CHD mechanisms supports the value of efforts to identify novel CHD paradigms. The indolent natural history of human atherosclerosis is a barrier to its understanding, as is the timeline between environmental or genetic triggers and the symptomatic phases of the syndrome. Deeper knowledge of the trajectory of atherosclerosis from its nascent stages through to clinical disease would enable more rigorous understanding of the contributing factors to each biological step. The ability to define the earliest transitions to disease during childhood might lead to powerful application of existing behavioral or pharmacological interventions during this critical period. Conversely, the ability to establish the absence of atherosclerosis would eliminate the inevitable contamination with subclinically affected individuals of control cohorts in epidemiology or genetic studies. These aspirational goals are currently hindered by the necessary focus on established CHD because the clinical events of the syndrome are complications of the mature plaque. Moreover, direct approaches to the in vivo study of atherosclerosis in youth are intrinsically challenging because of the inaccessibility of high-resolution coronary phenotypes. To enable the rigorous definition of biological trajectories in atherosclerosis will require tools to noninvasively measure the disease biology beyond the coronaries or carotids.

Defining New Translatable Phenotypes

Even accounting for gene–gene and gene–environment interaction, there is a significant unexplained heritability contribution to CHD. This undetected heritability has often been attributed to unascertained genetic information but remains elusive even in the context of complete genomes. Variants identified on a population level represent an averaged sample, concealing rare large-effect variants and channeling us toward genes of more modest individual impact. More prosaic reasons for our inability to detect genetic or environmental effects are likely to be the failure to measure fundamental underlying traits such as subclinical vascular abnormalities or to ascertain differential exposure to conditioning environmental factors without which even large heritable effects may simply be undetectable. Together these facts imply that one logical focus for transformational investigative efforts is the development of innovative phenotyping tools capable of defining disease throughout its trajectory and more rigorous and more comprehensive measurement of environmental challenges.

The importance of phenotyping is illustrated by the widely differing associations that can be made when looking at ostensibly the same underlying process (ie, atherosclerosis) across different parts of the arterial tree. The identification of novel quantitative traits present at the transition from wellness to disease, and therefore reflective of proximate biology in CHD, would enable early implementation of current prevention and stratification of CHD into etiologically distinct subtypes. Novel assays will be chosen for their biological relevance, their lack of redundancy, and the feasibility of scaling, all to ensure enrichment of biomedical information content, which is currently remarkably modest. Many factors including geographic and temporal variation, as well as effect sizes, will determine the scale necessary for these efforts.

Despite promising developments in functional imaging, we remain constrained in what we can learn about atherosclerosis from the coronaries or carotids themselves. Indeed, direct approaches may confine our thinking to a very discrete subset of biological models. Genetic susceptibly is driven by variants in genes with functions throughout the body, and understanding CHD will require a broad repertoire of vascular and extravascular phenotypes. This strategy would supplement existing indirect measures, such as flow-mediated dilation, with novel proximate traits, facilitated by new technology and inspired by an appreciation of the broad reach of shared causal mechanisms. Some new phenotypes will be merely correlative, but others may be driven by the core causes that underpin CHD, delivering insight through shared mechanisms. Ideally, these phenotypes by design would be translatable from humans to cellular and organismal biological models,[8] driving efficient mechanistic and therapeutic discovery.

The noninvasive detection of predisease states is not new, for instance, flow-mediated dilation itself; however, scalable technology capable of capturing metrics such as endothelial function and other physiological parameters is only now becoming available, enabling their incorporation into novel study designs. Much of this technology is wearable, and some is already integrated into daily life, thus enabling the passive capture of information, with greater temporal resolution, across the trajectory from health to disease and at population scale. Work to validate new parameters against established metrics and clinical end points is already well under way.

As society creates learning health systems, such biological data must stream digitally into personal repositories, alongside the existing, legacy clinical data sets. Together, these will form a suite of biologically rigorous orthogonal traits to monitor health or disease, to add stratifying dimensionality to classical syndromes, and to integrate care with discovery. An extant example in CHD may be the LRP6 syndrome identified by Mani et al,[15] which not only implicates lipoprotein-dependent signaling, but also demonstrates effects on cosegregating orthogonal phenotypes, both canonical (the metabolic syndrome) and noncanonical (osteoporosis) which may effectively parse atherosclerosis.

Measuring Environmental Exposures

Complementing our growing understanding of the genetic underpinnings of atherosclerosis, obtaining a better grasp on the specific environmental factors influencing disease (the exposome) to understand their diverse downstream consequences represents an opportunity to redefine most chronic syndromes and also carries great potential for discovery. Much as for novel phenotypes, it will be vital to capture this information in a fashion that is granular, continuous, and scalable. Only now is it becoming possible to effectively gather the vast amount of individual-level, unharvested data that surround each of us in our daily lives. Nutrition is but one area where technology might make a difference. The ability to move from time-limited, food frequency questionnaires to ongoing measurement of dietary intake at molecular resolution using quantified images, purchase data, and modern supply chain tracking will bring the opportunity to identify new triggers of CHD or other disorders.

Integrating the Data

To overcome perennial problems with cross-sectional data collection, where many confounders may modify each parameter even at homeostatic equilibrium, one design feature of next-generation phenotypes must be the introduction of standardized calibrating metadata in the form of discrete molecular or physical perturbations.

Combining individual measured exposures with high-resolution phenotypic data and clinical end points across multiple time scales will facilitate the detection of novel associations with chronic disease. Deviations in individual environmental exposures will be detectable at more minute levels, and because their effects will be measured on more precise quantitative traits, with direct correlates in animal models, this will allow these common factors to be used as perturbational challenges for relevant biological end points across the experimental spectrum from basic to clinical science.

Conclusions

The central One Brave Idea is to measure biology early enough to define health and its maintenance rather than just disease and to do so longitudinally in a way that enables the passive capture of disease trajectories. Combining such metrics with similarly high-resolution personal exposures will accelerate the implementation of existing preventative and therapeutic strategies, enable the deconvolution of new disease mechanisms upstream of the current final common pathways, and will help to drive the creation of a data return cycle capable of fueling truly learning health systems.

To achieve these aspirational goals, we have begun develop frameworks in which to collect, share and understand existing electronic health record data, biobanks, novel phenotyping data and of definitive exposures. Building new consensus taxonomies for subsets of disease will aid in the interpretation and translation of many traditional and nontraditional biomedical risk factors. A single program can only help to conceive of the redesign of the data inputs for biomedical science and begin to build an ecosystem for broader endeavors across academia and industry. A concerted redesign of biomedical data inputs offers numerous advantages, not least the ability to select informative dynamic phenotypes that can be passively collected, streamed directly into personal health records, combined with prespecified, shared metadata, and synthesized into meaningful objective personal biological histories with the potential for bidirectional translation. The timing is right for such system reconfiguration as care delivery also is undergoing revolutionary change. This unique opportunity to create integrated systems for prevention, care, and discovery will surely allow us to build some of the foundation we will need for truly precise or probabilistic medicine.

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