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''NEW STRATEGY IN OA''

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INTORDUCTION

On November fourth and fifth 2010 a gaggle of quite 100 international investigators gathered in Atlanta for the second Osteoarthritis (OA) Biomarkers Global Initiative workshop titled "Genetics and Genomics: New Targets in OA". The primary workshop came about in April 2009 and focused on in vitro (soluble) biomarkers whilst the third and final workshop will occur in 2012 and can specialize in imaging biomarkers. The OA Research Society International (OARSI) has organized the workshops. Additionally to OARSI, the National Institute of Arthritis, Musculoskeletal and Skin Diseases, the Arthritis Foundation, Amgen, Genzyme, the American Orthopedic Society for medical specialty and Pfizer sponsored the second meeting. it had been clear from this meeting that experiments within the genetics, epigenetics and genomics of OA, are yielding valuable insights into the etiology of this heterogeneous disease but that much still has to be learnt. Combining genetic insights with conventional biomarkers and imaging modalities may provide scientists with the improved tools to grasp this complex disease. With those tools in hand, clinicians and industry can develop protocols to ultimately improve patient care.

KEYWORDS

Biomarkers, Genetics, Epigenetics, Genomics.

Osteoarthritis (OA) and therefore the need for novel biomarkers

Over the last 20 years OA has come to be recognized as a fancy disease involving most, if not all, tissues of the joint. OA features a major heritable component, confirmed by epidemiological studies and now by molecular investigations. No disease modifying therapies have yet been developed, severely hampering disease management. Furthermore, OA remains principally diagnosed once radiographic changes in joint tissues are detected, often reflecting irreversible damage.

Like most typical, complex diseases, the genetic architecture of OA remains to be clarified. Molecular studies have, however, generated promising information about the genetic underpinnings; such novel insights may provide useful information on how the disease begins and progresses. Moreover, determining pre-clinical changes or abnormalities that reveal the disease closer to its place to begin might be accomplished at the molecular level with biomarkers. Strategies are required to detect and intervene early within the course of OA and to watch disease progression after treatment. Ultimately these strategies will help scientists understand the differences between diseased and normal joint tissues and thus satisfy the requirements of clinicians, industry, and patients. The Osteoarthritis Research Society International (OARSI) OA Biomarker Global Initiative aims to assist develop such biomarkers through a series of workshops designed to encourage international participation on a range of relevant topics.

The OARSI OA Biomarker Global Initiative

In 2009 funding for a series of three workshops was awarded to the OA Biomarker Global Initiative by the National Institute of Arthritis, Musculoskeletal and Skin Diseases (NIAMS). These meetings provide a forum for interchange of knowledge and concepts among members of the OA biomarker community by providing structure for biomarker discovery and use; providing resources to maneuver the sphere forward; providing white papers, guidelines, and validation to be used within the field; and maintaining momentum during this critical area. the primary workshop entitled “Biochemical Biomarker: Biology, Validation and Clinical Studies” was held in April 2009 in Bethesda, Maryland. Attendees focused on biochemical biomarkers of OA1.

Since the primary workshop, the world Initiative defined the sort of partnerships needed by investigators and funding organizations. The group also developed guidelines for sample collection, developed a web site for sharing information, and commenced an initiative between the u. s. Food and Drug Administration (FDA) and OARSI. From this latter initiative came guidelines for changes within the structure for FDA clinical studies.

Guidance associated with the OA field generally includes biomarker quantification; unmet needs within the biomarker field; and data on patient research.

The second workshop

In November 2010 over 100 delegates from across the world gathered in Atlanta for the second OARSI biomarkers workshop titled, "Genetics and Genomics: New Targets in OA". Additionally to NIAMS, the Arthritis Foundation, Amgen, Genzyme, the American Orthopedic Society for medical specialty, and Pfizer sponsored the meeting. The workshop focused on current research in genetic, epigenetic, and genomic studies of OA. Sessions assessed whether biomarkers derived from these approaches can realistically be used now or within the near future to spot and monitor people that are at increased risk for OA, or perhaps to spot those with enhanced protection from the disease.

Cohort studies

Ongoing debate has centered on how best to pick cases for OA genetic studies. Because OA may be a heterogeneous disease, more refined clinical phenotyping may help stratify the disease into homogeneous genetic and environmental subsets, thereby enhancing power of such genetic studies. Such subsets are perhaps not resolvable until unambiguous association data emerges that permits the identification of the phenotypes of carriers of risk DNA variant alleles.

The workshop therefore started with a discussion on current issues regarding case selection. within the first OARSI biomarkers workshop on biochemical markers, the anterior cruciate ligament (ACL) injury model was proposed to trace the onset of OA since it provides a transparent place to begin from which to observe events and progression to pre-radiographic and radiographic OA. for instance, refined reconstruction techniques for ACL tears allow athletes to return to the playing field. However, 10 years post-surgery, X-rays show evidence of arthritis in exactly some individuals, suggesting mechanical factors alone cannot account for OA. Such studies may reveal, during

a reasonable timeframe, who is most in danger for developing joint pathology and progression to OA and whether genetic factors play a modifying role.

In a preliminary study of West Point cadets with and without ACL injury within the pre- and post-clinical state, commercially available biomarkers of cartilage degradation and synthesis were measured. This unique cohort study was possible because of serial collections, since 1985, of medical and physical activity data from cadets, beginning at recruitment. Furthermore, ACL tears occur during this population at approximately 45 per 1,000. Perhaps most important was the difference in pre-clinical levels of both CPII and C2C within the ACL injured group as compared to controls, indicating that characteristics of joint metabolism may predispose, when physically challenged, to such an ACL injury.

Finally, a study was presented that compared serum and synovia biomarkers within the first several weeks after acute trauma to the ACL. during this pilot study, an outsized panel of biomarkers was analyzed following injury and treatment with intra-articular IL-1Rα. Data showed high initial levels of inflammatory proteoglycans and other matrix molecules followed by delayed collagen release. Perhaps indicating that early pro-inflammatory response to injury leaves a vital impact on long-term health consequences of the joint integrity. As collagen loss is taken into account irreversible very early treatment with agents to cut back collagen loss is also necessary to stop the onset of post-traumatic OA2.

Candidate genes and genome-wide association scans (GWAS)

Candidate gene and GWAS aim to supply insights into genes which will confer genetic risk or protection from OA. Thus far, OA appears to be highly polygenic with multiple risk alleles conferring small effects. Finding loci under these conditions require large sample sizes. Current large-scale consortia like arcOGEN and TREAT~OA are converging towards robust new OA targets with genome-wide significance ($P < 10-8$).Genetic studies in OA have thus far provided only a few of

strong signals, like single nucleotide polymorphisms (SNPs) at 7q223, 4, DIO25 and GDF56, 7. Two of those are known to own some effect on the skeleton. DIO2, a selenoprotein that converts intracellular inactive endocrine to its active form, regulates the expansion plate through internal secretion. GDF5, a member of the TGFβ superfamily of signalling molecules, is involved within the development, maintenance, and repair of bone and cartilage. Additional functional studies are necessary to elucidate the underlying molecular pathways, which can provide clues on possible druggable targets and/or biomarkers that allow early pre-clinical diagnosis of disease in carriers of those risk alleles8, 9. Gene markers accustomed predict the trajectory of OA don't necessarily should be polymorphisms. A session describing the role of epigenetics in common disease provided insights into how differences in epigenetic profiles of genes encoding proteinases, interleukins and growth factors may influence OA progression. Overall differences in organic phenomenon or epigenetic profiles can be useful markers or diagnostic tools.

More candidate genes and polymorphisms are expected as ongoing GWAS studies reach completion10. Each gene can potentially confer allelic heterogeneity (common and rare pathogenic variants), with rare genetic variants potentially having stronger and possibly distinctive effects on phenotype, and thus offering greater potential for intervention. Identifying robust polymorphisms related to OA won't provide an entire story. Many SNPs likely reside outside genes, might not be disease specific, nor be relevant to transcripts expressed in joints. Also, associated SNPs may reside inside genes whose function isn't yet understood. Thus, functional studies are critical. Functional genomic pipelines will elucidate molecular pathways underlying OA etiology and thus facilitate the invention of therapeutic targets. Functional genomic approaches will provide insight into the molecular background of those OA susceptibility loci and hopefully uncover disease mechanisms. Lastly, genetic contributions to the formation of joint shape may raise information provided by functional genetic approaches.

Challenges (the next step forward)

Data presented at the workshop showed progress in robust candidate genes, like GDF5, and reinforced the requirement to know the complex interplay between genetic and environmental causes of OA. To date, too few signals reach genome-wide significance whilst even fewer show compelling association across ethnic groups. Current OA susceptibility alleles are not providing enhanced risk prediction when combined with conventional risk factors like age, gender and body mass index (BMI). The elucidation of underlying pathways can supply such information as will collecting more data relevant to genetics, clinical features, and environmental risk factors. These new data will afford complete analyses of OA associated genetic variants.

The field of complex trait genetics is moving towards determining the role of low frequency and rare variants. The 1,000 Genomes Project11 and also the UK10K Project can provide OA studies with additional DNA variants to check whilst the stress must remain on large sample sizes to permit study replication and to also provide stratified analyses to both increase and specify attributable risk. Such second generation sequencing efforts aim to uncover rare genetic changes in tens of thousands of individuals across the world.

Challenges remain in many areas; like gene–environment interactions that are rarely captured in gene association studies and which complicate clinical utility. Furthermore, an oversized a part of heritability remains unexplained. Deep sequencing (whole genome, exome, and RNA-sequencing) may uncover additional rare genetic variation specific to OA susceptibility and should fill-in a number of the heritability gap. Also, biochemical markers or markers that denote joint shape are needed to produce quantitative phenotyping for genome-wide analyses of OA end phenotypes.

As the field moves towards sequence-based studies across the full genome, an improved idea of the total spectrum of genetic variants underlying OA may provide a therapeutic path for early intervention. Microarray expression profiles in cartilage have already provided insight into OA pathophysiology12, 13 whilst proteomic studies may pro-

vide insight into biomarkers with a synovial or cartilage origin14. The inaccessibility of joint tissue and also the invasiveness of drawing synovia, however, limits their use as routine biomarkers for OA unless they're released into urine or blood. Expression profiles in blood may provide an accessible new source of sensitive genomic biomarkers ciao as what's occurring within the damaged joint within reason mirrored in blood cells or serum. the same conundrum applies to epigenetic analyses – what's the proper tissue/s and time point in disease development to target?

Future genetic and genomic approaches will have to address disease heterogeneity; small effect sizes (odds ratios < 1.2); rare variants of possible large-effects; and epispastic and epigenetic effects. Functional studies will have to be performed on robust and replicated signals.

Lastly, the question of mixing multiple markers to assign risk for one individual must be addressed. Markers that may be combined include one risk entity (e.g., SNP), haplotypes for multiple variations in an exceedingly single gene, pathways for multiple expressed genes, metabolites, and proteins. The challenge will occur when multiple markers can't be “easily” adapted to supply an overall indicator of disease risk.

To meet all challenges put forth in Atlanta, the worldwide Initiative will establish a central clearance house on the OARSI website to permit an summary of current available studies and data, as an example upcoming GWAS of the National Institutes of Health sponsored OA Initiative (OAI) bio specimens (http://oai.epi-ucsf.org/datarelease/). This clearance house will provide an summary on available cohorts and thereby encourage collaboration so cohorts will be employed in different settings.

In addition, the worldwide Initiative will identify parameters in areas of common phenotypes, like OA in multiple joints, and ranging age groups. Diverse phenotypes will likely require equally diverse biomarkers for susceptibility, severity, and progression together with imaging approaches. Such an approach will help identify and follow

OA, beginning with the earliest molecular changes.

The third and final biomarkers workshop will occur in 2012, led by Professor David Hunter. This meeting will target imaging biomarkers. just like the second meeting, the ultimate workshop also will try to weave in what we've learnt from previous meetings to form an overall view of the present state of art of OA biomarkers. it'll be of interest to understand whether our understanding of the genetic, epigenetic, and genomic basis of OA has substantially progressed and whether it can integrate with conventional and imaging biomarkers to reinforce our ability to enhance clinical treatment of OA patients

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