Moleculaire reclassificatie van chronisch inflammatoire aandoeningen voor personalized medicine. Feit of fictie?

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THE PSORIATIC SPECTRUM

Psoriatic arthritis (PsA) is a disease most typically characterized by inflammation in the joints, spine, and enthesial-sites in a patient with a known history of psoriasis. The prevalence of PsA in the general population is presumed to be approximately 2 cases per 1000 individuals.[1,2] Whereas nearly all patients with PsA have psoriasis, it remains unclear why only ~20% of patient with psoriasis eventually develop PsA.[3] Although PsA was once considered relatively mild in comparison to the more prevalent articular inflammatory disease rheumatoid arthritis (RA), studies have shown that the burden of PsA on quality of life is equal to the burden of RA on quality of life.[4] In addition, patients with psoriasis and patients with PsA have an increased risk of cardiovascular morbidity and mortality, which is independent of traditional risk factors and presumably do to the disease itself.[5,6] The presence of systemic inflammation and other disease-specific factors in PsA is thought to underlie the accelerated development of atherosclerosis in these individuals.[7]

Unfortunately, PsA can be difficult to diagnose by non-specialists. This was well illustrated in a recent study[8] which examined patients with known psoriasis, none of whom were deemed to have PsA by their treating dermatologist. However, upon subsequent evaluation by a rheumatologist, ~30% of these patients in fact had a diagnosis of PsA. The delay in diagnosing PsA presumably contributes to the fact that over one-quarter of patients will already have irreversible joint damage upon their first visit to a rheumatologist.[9] In the last few decades there has been a remarkable turnaround in the treatment strategy for RA, in which early aggressive therapy is started to prevent irreversible joint damage and its subsequent symptoms. Such an approach is most likely an advisable strategy in PsA as well.[10] However, current standard treatment strategies incorporating disease-modifying anti-rheumatic drugs (DMARD's), originally developed for use in patients with RA, have shown disappointing results for patients with PsA: after two years of treatment only ~20% of patients will have reached remission and irreversible joint damage will still develop in ~50% of patients.[9]

These results emphasize the necessity to identify early (sub-clinical) PsA and identify which subset of patients is likely to respond to the first line of therapies we currently offer (i.e. DMARDS) and which subset of patients should instead be treated more aggressively using the more expensive second-line "biological-therapies" (e.g. tumor necrosis factor alpha inhibitors).

UMCU: COLLABORATIVE DERMATOLOGY AND RHEUMATOLOGY EFFORT

In the UMC Utrecht a collaborative effort is in place between the Department of Dermatology and the Department of Rheumatology and Clinical Immunology with the goal of improving psoriasis patient care, while at the same time allowing for meaningful, translational scientific research. All psoriasis patients are seen at a special psoriasis clinic in which care is provided by a psoriasis nurse and a dermatologist. In addition, a rheumatologist runs a parallel clinic that allows for the screening of

psoriatic arthritis in the psoriasis patients attending the clinic. All patients are offered such screening and recent publications from our group[11] have shown that in our academic setting, the use of simple questionnaires can be useful to aid the referral process. Treatment guidelines for treating psoriasis and for treating psoriatic arthritis do not always overlap and the needs of the individual patient are best met when these specialists deliver personalized medicine that goes beyond a skin-perspective-only or joint-perspective-only.[12] The specialized psoriasis clinic offers a unique opportunity for both psoriasis and psoriatic arthritis patients to participate in translational scientific research (see below). The strength of our research is greatly enhanced by the fact that participants are clinically well-characterized, for instance enabling an immunological comparison between patients with psoriasis limited to the skin versus psoriasis patients with concomitant arthritis.[13]

THE SYSTEMS MEDICINE APPROACH

PsA is thought to occur from the interaction of environmental factors with the immune system in individuals with polygenic susceptibility for the disease. In particular, there appears to be a problem in the innate immune response that leads to the development of PsA. On the basis of this disturbance in the first-line of the hosts' defence mechanism, it has been proposed that the subsequent occurrence of tissue-specific damage through micro-trauma or via the invasion of foreign pathogens in the skin, joint, bone, or enthesial-sites could explain the clinical manifestations of the disease.[14]

Because biological systems, such as the (innate) immune system, are able to maintain homeostasis under a multitude of circumstances, it can be difficult to pinpoint the exact interaction between the diverse genetic, epigenetic, and environmental factors that will ultimately cause a state of disease. This is specifically the case for PsA, in which all of these factors are known to play a role. The so-called "systems medicine approach"[15] aims to tackle this problem by integrating computational research with experimental medical research. This approach exploits the large amount of data collected from high-through-put technologies (called "omics" technologies) in order to analyse the different "layers" of the system of interest. Mathematical modelling is then used on the data in order to decode the sequence of events that define either normal or pathological functioning of that system. This method has proven fruitful in understanding the mechanism of successful vaccination.[16] Using this method, our group has recently made important discoveries in the disease systemic sclerosis.[17]

In our current research, we are examining all the "layers" of the immune response—the epigenetic modifications to deoxyribonucleic acid (DNA) (called epigenome), the set of RNA molecules that reveal gene expression profiles (called transcriptome), and the final product being the set of proteins (called proteome). The gene expression profile of a cell is of particular interest and can be revealed by RNA sequencing and analysing the sites on DNA that have become methylated, the latter modification being an important long-term regulator of gene expression and linked to the development of autoimmune disorders.[18] The final layer of the system explored is the cellular compartment of the immune system, in this case the function and phenotype of the white blood cells. The exploration of the interaction between these distinct layers can produce important discoveries, without needing prior knowledge about specific individual interactions between the subsets of the system. In a clinically well-defined cohort of psoriasis and PsA patients followed throughout time, the use of this systems medicine approach is well suited to identify new diagnostic and prognostic biomarkers. By unravelling the underlying pathogenesis, this approach could provide important insights into novel therapeutic targets.

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SAMENVATTING

Bij patiënten met psoriasis wordt de aandoening artritis psoriatica vaak gemist en zal de behandeling onvoldoende effectief blijken. In het UMC Utrecht werken de dermatologen en reumatologen samen op een psoriasisspreekuur, waarbij onder andere alle patiënten worden gescreend op de aanwezigheid van artritis psoriatica. Deze klinische samenwerking biedt tevens de mogelijkheid voor translationeel onderzoek. Door gebruik te maken van de zogenoemde systems medicine approach waarbij diverse lagen informatie van de afweercellen worden onderzocht en een grote hoeveelheid gegenereerde data vervolgens wordt geanalyseerd door computermodellen. Het doel is om diagnostische en prognostische biomarkers te identificeren en nieuwe therapeutische aangrijpingspunten te vinden voor deze patiënten.

SUMMARY

In this article, some aspects of toothpastes and contact Psoriatic arthritis (PsA) is currently under diagnosed and often resistant to treatment with traditional anti-rheumatic drugs, leading to increased morbidity and mortality. The UMC Utrecht has a specialized psoriasis clinic run by dermatologists en rheumatologists in which all patients are screened for psoriatic arthritis. This joint effort allows for performing meaningful, translation research. Indeed, the pathogenesis of PsA is not fully understood but thought to arise from the combination of genetic, epigenetic, and environmental factors. The so-called “systems medicine approach” uses high throughput technologies to help unravel the complex interactions between all these factors in order to better understand the specific pathways leading to this disease. The aim is to identify new diagnostic and prognostic biomarkers and novel therapeutic targets.

KEYWORDS

psoriasis – psoriatic arthritis (artritis psoriatica) – systems medicine

CONFLICT OF INTEREST

None