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Research paper

Epidemiology of transmissible diseases: Array hybridization and next generation sequencing as universal nucleic acid-mediated typing tools

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ABSTRACT

The magnitude of interest in the epidemiology of transmissible human diseases is reflected in the vast number of tools and methods developed recently with the expressed purpose to characterize and track evolutionary changes that occur in agents of these diseases over time. Within the past decade a new suite of such tools has become available with the emergence of the so-called "omics" technologies. Among these, two are exponents of the ongoing genomic revolution. Firstly, high-density nucleic acid probe arrays have been proposed and developed using various chemical and physical approaches. Via hybridization-mediated detection of entire genes or genetic polymorphisms in such genes and intergenic regions these so called "DNA chips" have been successfully applied for distinguishing very closely related microbial species and strains. Second and even more phenomenal, next generation sequencing (NGS) has facilitated the assessment of the complete nucleotide sequence of entire microbial genomes. This technology currently provides the most detailed level of bacterial genotyping and hence allows for the resolution of microbial spread and short-term evolution in minute detail. We will here review the very recent history of these two technologies, sketch their usefulness in the elucidation of the spread and epidemiology of mostly hospital-acquired infections and discuss future developments.

1. Introduction

The epidemiology of infectious diseases has classically been monitored using most if not all diagnostic technologies available to the microbiology laboratory. Obviously, culture for detection of microorganisms has been key and a mandatory first step in most of the classical epidemiological typing approaches. Beyond a positive culture, a broad variety of phenotypic and genotypic methods has been employed to gather a more refined insight in microbial variation that could be used to trace the dynamics of nosocomial carriage, cross-infection and real-life (hospital- and community-acquired) outbreaks of infection. Phenotypic markers have varied from classical biochemical data, different staining procedures coupled with microscopy, information on susceptibility to antimicrobial drugs, phage-mediated lysis or lysogeny profiles, electrophoretic protein profiles and several others including matrix-assisted laser-desorption time of flight mass spectrometry (MALDI TO MS) (Van Belkum et al., 2017). Genotypic analyses range from plasmid and genomic restriction fragment profiling and electrophoretic separation of macro-restriction fragments to isothermal amplification procedures, heteroplex PCR testing, array hybridization and (next generation) (genomic) sequencing (for reviews see Van Belkum et al., 2007 and Sabat et al., 2013). Given their current importance, the latter two technologies will be discussed in more detail in the present review.

2. Array hybridization for epidemiological characterization

2.1. Technical aspects and types of arrays

Arrays can be composed of a diversity of fundamentally different molecular categories and examples include those with peptides and/or proteins, lipids, sugars and antibodies. The best known and most used

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nucleic acid arrays or DNA chips containing collections of DNA and/or RNA molecules (either synthetic or natural and also including peptide nucleic acids in some specific cases) are known in at least two different categories: those where the nucleic acid is synthesized in vitro directly on a small predefined region of a solid support and the other category consisting where the nucleic acid molecules are spotted to a targeted region, also with high accuracy. Probes used can be as short as oligonucleotides but may also be representing extensive genomic domains or regions. A wide variety of elegant biological, chemical and physical procedures have been adapted to facilitate these two processes (for a review see Booth et al., 2000). The number of different molecules included in an array can vary from between a couple of dozens to hundreds of thousands of different nucleic acid moieties. For instance, the use of an array harboring 95.000 random 13-meric oligonucleotides allowed for overall genotypic characterization of essentially any genomic DNA preparation (Pasquer et al., 2010).

Hybridization reactions between covalently attached and dissolved nucleic acid molecules occur near the surface of the microarrays usually at the interface of liquid and solid phases. The solution in which the solid array support is immersed contains dissolved and often labelled nucleic acid molecules of which the nucleotide sequence is potentially complementary to that of one or more of the immobilized nucleic acid molecules. In case where the solubilized nucleic acids are labelled and where binding takes place between probe and target, hybridization can be detected by visualization of such different labels on the surface of the DNA chip (e.g. Schulze et al., 2012). Again, a wide variety of labelling techniques for genomic DNA, plasmids or PCR- or otherwise-amplified DNA molecules have been described. In addition, several electrochemical read-out systems have been proposed but these have not yet known a successful academic or commercial exploitation. Next to all the requirements relating to laboratory activities including sensitive and specific positive and negative controls there is in most cases also a need for data capture (often photography or scanning) and automated data processing. Especially in clinical applications signals need to be translated into figures and then into results regarding the absence, presence or constitution of a certain nucleic acid marker (Kokocinski et al., 2005; Woo et al., 2005). In combination with laboratory automation and standardization, the development of data interpretation forms the basis of routine application of tests with an intrinsically complicated build-up.

Different DNA microarray systems can be used for monitoring the absence or presence of certain nucleic acid sequences in a given sample, for studying gene expression in a massive parallel fashion but also for detecting differences between even closely related molecules. DNA array systems for picking up specific point mutations, insertions, deletions or the selective presence of entire genes or alleles thereof have been proposed and used for molecular diagnostic purposes. When the reaction conditions and the bioinformatics design are precisely balanced, arrays can be used to detect single point mutations between different molecules (RNA, DNA) of significant length i.e. several hundreds of base pairs and structure (double stranded and single stranded). Obviously, this technology has been well exploited in a variety of research domains and, of course, in clinical microbiology as well (see the excellent reviews by Miller and Tang, 2009; Chandler et al., 2012 and Kumar, 2009). Fundamental and applied research into genomic variation and evolution has profited extensively from array-based testing (Nsofor, 2014). Between 2000 and 2008 the number of papers published increased from just a few to about 500 per year in the domain of clinical microbiology. More and more commercial products on different platforms and readout systems became available over this period as well and still a large variety of array products can be purchased for diagnostic purposes with a meanwhile reasonable price. Most recently classical arrays have been supplemented by bead arrays, be it in liquid or in conjunction with solid phase beads (Hathout, 2015). In principle, given the sensitivity and specificity of array hybridization, subtle genomic differences can be detected between different isolates of a single bacterial species (e.g. Gardner et al., 2013). Using the most modern of technologies, entire genomes can be covered at a nearly base-by-base level in a limited amount of time and with a sensitivity of 10 cells per assay (Zhang et al., 2008; Wiesinger-Mayr et al., 2007). Obviously, sample preparation and whole genome amplification procedures are very important components of such sensitive approaches. The application most reported upon, however, is the one where antibiotic resistance genes are specifically targeted (Batchelor et al., 2008; Monecke et al., 2011; Leinberger et al., 2010; Frye et al., 2010; Lascols et al., 2012; Leski et al., 2013; Braun et al., 2014; Taitt et al., 2015). Hence, the technology was deemed suitable for epidemiological tracking of infectious agents although in several cases specific software packages for the correct interpretation of the sometimes complicated data had to be developed (Jupiter et al., 2009).

2.2. Species targeted

Within the field of clinical microbiology essentially all classes, genera and species of organisms and a good deal of their phenotypes have been diagnostically addressed using array technology (Herrera-Rodriguez et al., 2013). Several species have been included in epidemiological typing studies, both from the human and veterinary perspective (Garaizar et al., 2006; Beena et al., 2016). These include, for example, *Clostridium difficile* (Gawlik et al., 2015), *Streptococcus pneumoniae* (Kamng'ona et al., 2015), *Pseudomonas aeruginosa* (Ballarini et al., 2012), *Listeria* spp. (Hmaïed et al., 2014), *Neisseria meningitidis* (Corless et al., 2008), *Chlamydia* spp. Sachse et al., 2005; Sachse et al., 2008; Ruettger et al., 2011) *Acinetobacter baumannii* (Ko et al., 2008), *Klebsiella pneumoniae* (Viau et al., 2012), *Campylobacter* spp. (Marotta et al., 2013), *Bordetella pertussis* (King et al., 2010), *Legionella pneumoniae* (Cazalet et al., 2008; Petzold et al., 2017), *Mycobacterium* spp. (Ruettger et al., 2012), *Salmonella* spp. (Braun et al., 2012), *Yersinia pestis* (Lowell et al., 2015; Wang et al., 2007) and many others. For instance, the complete genome sequence for the *P. aeruginosa* reference strain PAO1 was used for the development of a commercial Affymetrix array representing > 5000 genes (Wolfgang et al., 2003). Initial analyses show a uniform presence of virulence genes among clinical isolates but variable segments suited for typing were localized as well (Wiehlmann et al., 2007). Below follows an incomplete list of several key human pathogens responsible for community- and hospital-acquired infections (CAI, HAI) and for which substantial array typing studies have been published.

2.2.1. *Staphylococcus aureus*

S. aureus is a very frequent agent of infection in humans and animals. It lives in close interaction with its host usually as a colonizer of the nasal cavity and the skin. *S. aureus* is present in the nose of approximately one third of mankind (Wertheim et al., 2004; Wertheim et al., 2005). However, it can also cause a wide variety of infections, ranging from minor skin- and soft tissue infections to life-threatening conditions such as necrotizing fasciitis, sepsis or pneumonia. Because of limited therapeutic options, methicillin resistant *S. aureus*, MRSA, is especially notorious. When colonizing, resident populations of *S. aureus* may evolve, dependent on the frequency of ecological and biological bottlenecking (Golubchik et al., 2013; Van Belkum, 2016). Both MSSA and MRSA spread relatively easily between humans and nosocomial outbreaks of staphylococcal infections are well documented. Given its clinical importance, detailed epidemiological studies and investigations that target the detection of resistance and (its many) virulence genes have been regularly presented. The use of array hybridization has been very frequent in this respect.

Affymetrix arrays were among the first used for the epidemiological typing of *S. aureus*. Initial studies showed that multi-locus sequence typing (MLST) performed using such DNA chips was completely conform classical typing methods (Van Leeuwen et al., 2003). This was confirmed by Cassat et al. (2005) who used two different array types

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