Clinical glycomics of antibodies by mass spectometry

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Addendum

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Nederlandse samenvatting

De eiwitten die in het menselijk bloed circuleren hebben een scala aan verschillende functies en eigenschappen. Onder deze functies vallen, bijvoorbeeld, het coördineren van biologische processen, het synthetiseren of bewerken van andere moleculen en de bescherming van het lichaam. Bepaalde eiwitmodificaties zijn van groot belang voor het goed kunnen functioneren van de eiwitten. Een belangrijk voorbeeld hiervan is de verscheidenheid aan suikerketens (glycanen) die op specifieke plaatsen aan een eiwit vast kunnen zitten. Deze suikergroepen zijn erg divers, zowel als het gaat om de compositie (de monosacchariden waar het glycaan uit is opgebouwd), als de structuur (de manier waarop de monosacchariden aan elkaar gebonden zijn). Veranderingen in de glycaan compositie en/of structuur worden waargenomen tijdens (patho)fysiologische processen, zoals veroudering, zwangerschap, menopauze en ziekten. Het is dus aannemelijk dat het bestuderen van deze glycanen inzicht zou kunnen geven in de biologische processen die in het lichaam plaatsvinden. Deze kennis kan mogelijk een rol spelen in de ontwikkeling van nieuwe farmaceutische en klinische producten, bijvoorbeeld door het blootleggen van nieuwe therapeutische doelwitten of ziekte-specifieke signaalstoffen.

Antilichamen, oftewel immunoglobulinen, zijn eiwitten die een belangrijke rol spelen in de bescherming van het lichaam tegen ziekteverwekkers. De functionaliteit van deze eiwitten is vaak voor een groot deel afhankelijk van de glycosylering op het *fragment crystallizable* (Fc) gedeelte van het antilichaam. Het is daarom van belang dat er betrouwbare methoden beschikbaar zijn die de antilichaamglycosylering in kaart kunnen brengen. Dit is echter niet eenvoudig, omdat antilichamen meerdere glycosyleringslocaties kunnen hebben, deze locaties niet altijd een glycaan bevatten en de glycanen vele, vaak isomere, structuren aan kunnen nemen. Het onderzoek, dat in dit proefschrift beschreven wordt, focust zich enerzijds op de ontwikkeling van massa spectrometrische methoden om antilichaamglycosylering te bekijken en anderzijds op de toepassing van deze methoden voor de karakterisering van antilichaamglycosylering van specifieke organismen, lichaamsvloeistoffen en/of medische condities.

In **Hoofdstuk 1** wordt eiwitglycosylering geïntroduceerd. In het bijzonder worden de glycaaneigenschappen en -functies voor immunoglobuline G (IgG) beschreven. Verder worden ook de massaspectrometrische methoden behandeld waarmee eiwitglycosylering in kaart kan worden gebracht. Hierbij wordt de nadruk gelegd op de methoden die in het onderzoek van dit proefschrift worden gebruikt. Deze zijn gebaseerd op het analyseren van glycopeptiden met behulp van *matrix assisted laser desorption/ionization* (MALDI)-*time-of-flight* (TOF)-massaspectrometrie (MS) en *electrospray ionization* (ESI)-TOF-MS. ESI-TOF-MS werd gebruikt in combinatie met vloeistofchromatografie (LC) om complexe mengsels te scheiden voordat deze de MS bereiken.

De twee, bovengenoemde massaspectrometrische methoden verschillen onderling in snelheid, resolutie en informatiedichtheid van de verkregen data. De MALDI-TOF-MS methode is relatief gemakkelijk en snel in gebruik. Echter, als een glycopeptiden monster wordt gemeten zonder verdere monstervoorbewerkingsstappen, kan dit resulteren in een vertekend beeld van de gesialyleerde glycoconjugaten. Dit komt doordat de siaalzuren instabiel zijn tijdens het ionisatieproces en doordat hun negatieve lading zorgt voor ongelijke ionisatie tussen gesialyleerde en ongesialyleerde glycaanstructuren en de formatie van zouten met alkalimetalen. In **Hoofdstuk 2** wordt een methode beschreven voor de derivatisering van IgG glycopeptiden. Deze methode zorgt voor de stabilisatie van de gesialyleerde glycoconjugaten. Bovendien zorgt de beschreven derivatisering ook voor twee verschillende producten voor siaalzuren die respectievelijk α2,3- of α2,6-gelinkt zijn aan de voorgaande galactoses. Hierdoor kunnen siaalzuurisomeren van elkaar onderscheiden worden op basis van de MS metingen en zonder voorgaande chromatografische scheiding.

Er is een groot repertoire aan voorgaande studies waarin IgG Fc glycosylering wordt beschreven onder verschillende klinische omstandigheden. Echter worden de functie en regulatie van IgG Fc glycosylering nog steeds niet volledig begrepen. Daarnaast zijn de meeste van deze studies uitgevoerd met monsters van volwassenen, terwijl er over IgG glycosylering in kinderen nog maar weinig bekend is. In **Hoofdstuk 3** wordt de methode die in **Hoofdstuk 2** is ontwikkeld, toegepast voor de analyse van IgG Fc glycopeptiden die zijn verkregen uit het plasma van gezonde kinderen en pasgeborenen. In deze studie werden verbanden aangetoond tussen IgG glycaaneigenschappen en de leeftijd van de kinderen. Deze resultaten dienden als uitgangspunt om ziekte gerelateerde glycaanveranderingen in kinderen verder te bestuderen.

Om meer inzicht te krijgen in hoe IgG Fc glycosylering gereguleerd wordt, wordt er in **Hoofdstuk 4** gekeken naar de IgG glycosylering van kinderen die behandeld zijn met een hematopoietische stamceltransplantatie. Hierbij worden patiëntmonsters van voor en na de transplantatie met elkaar vergeleken. Verder worden de patiëntmonsters vergeleken met de monsters van de donoren van voor transplantatie. Deze studie liet zien dat het micromilieu van de B cellen, de cellen die verantwoordelijk zijn voor de antilichaam productie, een grote invloed heeft op de glycaanstructuren die op de IgGs worden gevonden.

Eén aspect van het gebruik van antilichaamglycosylering in een klinische toepassing is de mogelijkheid om zieke individuen te onderscheiden van gezonde. Echter is het ook zeer relevant om iets te kunnen zeggen over zekere sub-varianten van bepaalde ziektebeelden of de ernst van een aandoening. Dit bied namelijk de mogelijkheid om een ziekte en/of behandeling van een patiënt te volgen en de behandeling op individuele wijze aan te

passen. In **Hoofdstuk 5** wordt IgG Fc glycosylering bestudeerd van kinderen die lijden aan meningokokken sepsis. Naast glycaaneigenschappen die geassocieerd konden worden met de ziekte, werden er glycaanprofielen gevonden die specifiek waren voor de ernst van de ziekte. IgG glycaaneigenschappen lijken, wanneer deze gemeten worden kort nadat een patiënt is opgenomen in het ziekenhuis, een voorspellende waarde te hebben voor de uitkomst van de ziekte.

In **Hoofdstuk 6** wordt IgG Fc glycosylering bekeken in de context van inflammatoire darmziekten (IBD). Ook hier konden glycaanprofielen worden gevonden die correleerden met ziekte eigenschappen, zoals het IBD subtype (ziekte van Crohn en colitis ulcerosa) en de progressie. Verder werd ook het effect van een behandeling (met medicatie of operatie) teruggevonden in het IgG glycaanprofiel van de patiënten.

Het overgrote deel van de functionele studies naar IgG Fc glycosylering is uitgevoerd in muizen. Hoewel het gebruik van de muis als modelorganisme voor de mens een aantal grote voordelen heeft, zoals de mogelijkheid om de muizen genetisch te manipuleren, moet er rekening mee gehouden worden dat de glycosylering die in muizen gevonden wordt niet precies hetzelfde is als die van de mens. In **Hoofdstuk 7** wordt een systematische studie gepresenteerd waarin de IgG Fc glycosylering van verschillende muizenstammen met elkaar vergeleken wordt. Dit wordt gedaan op een glycaanlocatie- en eiwit-specifieke manier, via glycopeptide analyse met LC-ESI-TOF-MS.

In **Hoofdstuk 8** komt, naast IgG, ook een ander antilichaam aan bod: immunoglobuline A (IgA). Dit antilichaam wordt, samen met IgG, geïsoleerd uit humaan speeksel en bloedplasma, waarna er een LC-ESI-TOF-MS platform gebruikt wordt om de glycosylering van deze eiwitten te bestuderen. Hiermee werd aangetoond dat de IgA glycosylering in plasma en speeksel van elkaar verschilt, wat er op duidt dat de regulatie van de antilichaamglycosylering afhangt van de locatie waar deze worden geproduceerd.

Concluderend, en zoals verder bediscussieerd in **Hoofdstuk 9**, bied dit proefschrift nieuwe massaspectrometrische methoden die gebruikt kunnen worden voor het bestuderen van antilichaamglycosylering. Deze methoden werden toegepast op klinische monsters om het toekomstig gebruik van antilichaamglycosylering in de kliniek vooruit te brengen. Er is verder onderzoek nodig naar de mechanismen die er voor zorgen dat antilichaamglycosylering veranderd tijdens bepaalde fysiologische condities en naar het effect van deze veranderingen op een immuunrespons. Ook zullen er nog stappen gezet moeten worden op technologisch gebied. Het is voor de klinische toepassing van de bevindingen namelijk essentieel dat er een relevante deelverzameling van glycaanstructuren op een robuuste manier gemeten kan worden, over een lange tijdsperiode en met variërende monstereigenschappen (zoals eiwit concentratie en

monster matrix). Hiervoor zou de implementatie van interne standaarden in de massaspectrometrische werkprocessen weleens essentieel kunnen zijn.

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Dear reader, thank you for ending up reading my thesis. Even if you went straight to the acknowledgments, I am very happy you are here! Because this is the place where I can truthfully thank all people that were important during the past four years. The ones who taught me, supported me, motivated me and made these years an amazing experience.

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In the years after I started, numerous people joined our dynamic group, always resulting in a new composition of fun and inspiring scientists. Thank you all a lot for the "gezelligheid" in the office, the good discussions and your help with my research.

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Curriculum Vitae

Noortje de Haan was born on the 27th of January, 1991 in Amsterdam, The Netherlands. Both at primary and secondary school she received Montessori-based education and in 2009 she graduated from the Montessori Lyceum Amsterdam. She followed the interdisciplinary Bachelor's study of Pharmaceutical Sciences at the Vrije Universiteit Amsterdam. In addition, she enrolled in the VU Honours Programme to extend the interdisciplinary nature of her studies. She graduated *cum laude* for her Bachelor's degree in 2012 and started the Master's studies in Drug Discovery and Safety, also at the Vrije Universiteit Amsterdam. At this time, it became clear that Noortje had a strong fascination for the processes going on in the human body and specifically for how these could be studied with analytical chemical technologies. During her Master's studies, she specialized in Biomarkers and Clinical Chemical Analysis. Furthermore, she enrolled in the COAST MSc+ program, part of the "Topsector Chemie" talent program. Her literature thesis described the use of analytical technologies for the analysis of substance adsorption to medical implants and was performed in collaboration with DSM, under the supervision of Dr. Maarten Honing. Furthermore, she performed her internship at the Leiden University Medical Center, Center for Proteomics and Metabolomics (CPM), under the supervision of Dr. Karli Reiding and Prof. Dr. Manfred Wuhrer. This was the time Noortje first encountered the world of glycosylation and its application in medicine, something she did not let go of for the years to come. Following her *cum laude* graduation in 2014, she started a PhD program at the CPM, under the supervision of Dr. David Falck and Prof. Dr. Manfred Wuhrer. During her four years of PhD project she worked on the development and application of various mass spectrometry-based methods for the analysis of (antibody) glycosylation, which resulted in her learning a lot, twelve (co-authored) publications and this thesis. After the completion of her thesis, Noortje continued her postdoctoral research at the CPM.

List of publications

First author papers

1) **Linkage-Specific Sialic Acid Derivatization for MALDI-TOF-MS Profiling of IgG Glycopeptides**
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Co-authorships

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