Wrapping up : nidovirus membrane structures and innate immunity

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SAMENVATTING

Virussen kunnen levensbedreigende infecties veroorzaken, ondanks het feit dat ze relatief simpel in elkaar zitten. Het virusdeeltje bestaat uit het genoom dat is ingepakt in een of meerdere eiwitten. Bij veel virussen bevat het deeltje ook een membraan, met daarin verankerd de eiwitten waarmee het virusdeeltje aan een receptor kan binden om een gastheercel te infecteren. Na dit moment van infectie, interacteren virussen op allerlei vlakken met de gastheercel om uiteindelijk nieuwe virusdeeltjes te kunnen maken. Dit stapsgewijze proces wordt de replicatiecyclus genoemd, en tussen virusfamilies en -groepen bestaat aanzienlijke variatie waar het de details van deze cyclus betreft. In het geval van de positiefstrengige (+) RNA-virussen bestaat het virale genoom uit een enkelstrengs mRNA molecuul dat direct na het binnendringen in de cel wordt afgelezen door ribosomen om zo de eerste virale eiwitten te produceren. Deze eiwitten zorgen ervoor dat het genoom wordt vermenigvuldigd en kan worden verpakt in nieuwe virusdeeltjes.

Dit proefschrift richt zich op de een specifiek aspect van de replicatie van de arterivirussen en de coronavirussen (twee +RNA-virusfamilies), namelijk de vorming van zogenaamde replicatieorganellen in het cytoplasma van de geïnfecteerde cel. Arterivirussen en coronavirussen zijn evolutionair verwant en behoren tot de orde van de nidovirussen. Arterivirussen veroorzaken vooral problemen in de veterinaire wereld, terwijl coronavirussen ook humane infecties kunnen veroorzaken. De bekendste coronavirussen zijn het severe acute respiratory syndrome coronavirus (SARS-CoV) en Middle East respiratory syndrome coronavirus (MERS-CoV), die beiden dodelijke respiratoire infecties in de mens kunnen veroorzaken. Hoewel het genoom van coronavirussen twee tot drie keer groter is dan dat van arterivirussen, is de genoomorganisatie en replicatiecyclus van deze twee virusfamilies in grote lijnen vergelijkbaar. De voor mensen ongevaarlijke arterivirussen worden daarom mede gebruikt als model om de replicatiecyclus van levensbedreigende coronavirussen in kaart te brengen.

+RNA virale replicatieorganellen zijn structuren die aangemaakt worden in de geïnfecteerde gastheercel op basis van een samenspel tussen virale en cellulaire spelers. De basis van de replicatieorganellen wordt gevormd door membranen die 'gestolen' worden van de gastheercel. De transformatie van deze membranen tot unieke membraanstructuren wordt aangestuurd door specifieke +RNA virale transmembraaneiwitten, vermoedelijk in nauwe samenwerking met gastheerceleiwitten. De omvangrijke wetenschappelijke literatuur over +RNA-virale replicatieorganellen wordt samengevat in **hoofdstuk 2**. In de wetenschappelijke literatuur is veel gespeculeerd over de functie van deze replicatieorganellen tijdens virusinfectie. Ten eerste wordt gedacht dat deze structuren een "micromilieu" vormen ter bevordering van de enzymatische reacties die nodig zijn tijdens de reproductie van het virale genoom. Ook zouden deze structuren kunnen bijdragen aan de regulatie van de replicatiecyclus, door verschillende processen te compartimentaliseren. Tot slot wordt aangenomen dat de replicatieorganellen ervoor zorgen dat de gastheercel het binnengedrongen virus niet (of pas later) kan herkennen. De structuren zouden een soort schild vormen om het virale genoom af te schermen van het zogenaamde aangeboren

immuunsysteem. Replicatieorganellen worden niet alleen in nidovirus- geïnfecteerde cellen gevormd, maar in alle eukaryote cellen die geïnfecteerd zijn met een +RNA-virus, hoewel de soort membraanstructuren en het als membraandonor gebruikte cellulaire compartiment sterk kunnen vetschillen. De vorming van deze membraanstructuren is daarmee één van de meest karakteristieke elementen van de replicatiecyclus van deze grote virusgroep. Voorbeelden van de replicatieorganellen van arterivirussen en coronavirussen zijn afgebeeld in **hoofdstuk 2** figuur 2 en 4. Arterivirus-geïnduceerde replicatieorganellen bestaan uit "double-membrane vesicles" (DMVs), gesloten blaasjes die zijn omgeven met twee gepaarde membranen (**hoofdstuk 2**, figuur 2B). Deze DMVs zijn via hun buitenmembraan met elkaar verbonden en vormen zo een netwerk. Coronavirussen vormen naast DMVs ook nog enkele andere membraanstructuren zoals "convoluted membranes", "spherules" en "vesicle packets".

Bij nidovirussen wordt de vorming van de replicatieorganellen geïnduceerd door de virale eiwitten die gemaakt worden door translatie van het virale genoom. Deze eiwitten worden gemaakt als onderdeel van twee lange poly-eiwitten, die intern gekliefd worden tot losse eenheden (nonstructural proteins, nsps) door proteases die in deze poly-eiwitten aanwezig zijn. Doordat de replicatiecyclus van een virus een complex proces is, is het lastig om specifieke onderdelen van de virale replicatiemachine te modificeren zonder dat de replicatie zelf verstoord wordt of verloren gaat. Door bijvoorbeeld mutaties aan te brengen in de nsps die de vorming van replicatieorganellen induceren zou men kunnen bestuderen hoe de organellen gevormd worden en welke gastheercelfactoren daarvoor nodig zijn. Maar als door zulke mutaties essentiële aspecten van de replicatiecyclus niet meer functioneren worden de virale eiwitten die de vorming van membraanstructuren aansturen überhaupt niet meer gemaakt, waardoor er geen replicatieorganellen worden gevormd. **hoofdstuk 3** beschrijft onderzoek naar de vorming van arterivirus replicatieorganellen. Sinds 2001 was bekend dat de expressie van twee arterivirale nsps (nsp2 en nsp3) voldoet om - buiten de context van virusreplicatie - de vorming van membraanstructuren te induceren. Deze 'surrogaat'structuren lijken sterk op de replicatieorganellen die gevormd worden tijdens arterivirusinfectie. Omdat nsp5, naast nsp2 en nsp3, het enige andere arterivirale transmembraan nsp is, was het aannemelijk dat nsp5 ook een rol speelt in de vorming van DMVs, en ook dit is in dit hoofdstuk bestudeerd. De DMVs die werden gevormd na gezamenlijke expressie van nsp2, nsp3 en nsp5 waren kleiner en uniformer, maar de globale structuur van de DMVs veranderde niet. Dit wijst erop dat nsp5 waarschijnlijk een regulerende rol heeft. Ook is in dit onderzoek een driedimensionale reconstructie gemaakt van de 'surrogaat' DMVs, om meer inzicht te krijgen in hun biogenese. Daaruit bleek dat waarschijnlijk eerst twee membranen worden gepaard, die daarna tot DMVs worden getransformeerd.

Het was lang onbekend welke coronavirale eiwitten nodig zijn om DMVs (en de andere structuren van het coronavirus replicatieorganel) te vormen. In 2013 beschreven Angelini *et al*. dat voor SARS-CoV nsp3, nsp4 en nsp6 nodig zijn voor de vorming van DMVs. Coronavirus nsp3, nsp4 en nsp6 zijn te vergelijken met arterivirus nsp2, nsp3 en nsp5 (zie ook **hoofdstuk 2**, figuur 1). In **hoofdstuk 4** laten we echter zien dat voor zowel SARS-CoV

als MERS-CoV expressie van nsp3 en nsp4 voldoende is om DMV-vorming te induceren, en dat MERS-CoV nsp6 geen rol lijkt te spelen bij DMV-vorming. Ook dit onderzoek werd uitgevoerd met behulp van gedetailleerde driedimensionale reconstructies op basis van elektrontomografie, en laat zien dat arterivirussen en coronavirussen vergelijkbare mechanismen gebruiken om DMVs te vormen. Zoals eerder vermeld maken de coronavirus nsps deel uit van een groot poly-eiwit, dat door interne proteases tot individuele nsps wordt gekliefd. Deze proteases bevinden zich in nsp3 en nsp5. In dit onderzoek is ook gekeken naar de rol in DMV-vorming van de klieving tussen nsp3 en nsp4 door het protease in nsp3. De klieving tussen nsp3 en nsp4 bleek essentieel om DMV-vorming op gang te brengen. Als deze klieving werd geblokkeerd, werden de membranen nog wel gepaard, maar in plaats van DMVs accumuleerden dubbele membranen, vaak in de vorm van concentrische structuren. Deze resultaten geven aan dat de klieving van het virale poly-eiwit een integrale rol kan spelen in de regulatie van de vorming van +RNA virale replicatieorganellen.

Cellen hebben een breed scala aan sensoren om de aanwezigheid van een virus te detecteren. Deze sensoren herkennen bijvoorbeeld het virale genoom, virale eiwitten of virusdeeltjes. Herkenning is gebaseerd op bepaalde ongebruikelijke moleculaire patronen, en is niet gericht op een specifiek pathogenen, zoals dat wel het geval is bij de adaptieve immuunrespons. Als een cel een binnengedrongen virus heeft gesignaleerd, wordt het aangeboren immuunsysteem geactiveerd. Dit zorgt ervoor dat zowel in de geïnfecteerde cel als in nabijgelegen cellen een antivirale modus aangeschakeld wordt, die deze cellen moeilijker te infecteren maakt en virusreplicatie remt. Dit signaal wordt onder meer overgedragen door interferon eiwitten. Ook zorgt de antivirale modus ervoor dat witte bloedcellen worden gerekruteerd om het adaptieve immuunsysteem te activeren. Deze mechanismen, en hoe ze gereguleerd worden, worden toegelicht in **hoofdstuk 5**. Om toch te kunnen repliceren hebben virussen verschillende methoden ontwikkeld om te voorkomen dat ze herkend worden of om de cellulaire respons te blokkeren of te vertragen. Dit resulteert in een constante wapenwedloop tussen het aangeboren immuunsysteem en virussen.

De resultaten beschreven in **hoofdstuk 6** toonden aan dat het aangeboren immuunsysteem arterivirus DMV-vorming, door expressie van virale eiwitten geïnduceerd, kan remmen. In dit onderzoek zijn cellen die arterivirus nsp2 en nsp3 tot expressie brengen behandeld met interferon om de antivirale modus te activeren. Aangezien interferonbehandeling virusreplicatie op meerdere fronten remt, is dit onderzoek uitgevoerd buiten de context van virusinfectie om specifiek een effect van het aangeboren immuunsysteem op DMV-vorming te kunnen onderzoeken. In deze proefopzet zorgde interferonbehandeling ervoor dat minder cellen DMVs vormden. Daarnaast werden er na interferon behandeling meer gepaarde membranen gevonden (die geen DMVs vormden) in vergelijking met onbehandelde cellen. Deze bevindingen wijzen op remming van DMV-biogenese door het aangeboren immuunsysteem. De antivirale respons die door interferon wordt geactiveerd leidt tot verhoogde expressie van minstens driehonderd verschillende genen. Van drie van deze genen (CH25H, viperin en PLSCR1) is getest of ze invloed hebben op DMV-vorming door arterivirus nsp2 en nsp3, omdat elders vergelijkbare effecten van hun

genproducten waren beschreven. CH25H, viperin en PLSCR1 bleken echter niet betrokken bij de remming van arterivirale DMV-vorming door het aangeboren immuunsysteem, wat suggereert dat dit gebeurt via een tot op heden onbekend mechanisme.

Het werk in dit proefschrift verschaft nieuwe inzichten in de biogenese van replicatieorganellen van arterivirussen en coronavirussen. Ook is nu duidelijk dat cellen actief proberen de vorming van deze replicatieorganellen tegen te gaan. Als in toekomstig onderzoek het mechanisme van de remming van DMV-vorming door het aangeboren immuunsysteem opgehelderd wordt, kan deze kennis bijvoorbeeld gebruikt worden om selectieve antivirale strategieën te ontwikkelen.

CURRICULUM VITAE

Diede Oudshoorn werd 5 februari 1989 geboren te Warmond. In 2005 behaalde hij zijn gymnasiumdiploma aan het Stedelijk Gymnasium in Leiden. Vervolgens begon hij aan de opleiding Biomedische Wetenschappen aan de Universiteit Leiden. Tijdens de bachelor fase nam hij deel aan een uitwisselingsprogramma met het Karolinska Instituut in Stockholm, Zweden. Tijdens de onderzoeksspecialisatie in de master fase heeft Diede zijn eerste stageproject uitgevoerd bij de afdeling Medische Microbiologie (LUMC) onder begeleiding van Kazimier Wannee, M.Sc. en dr. ir. Marjolein Kikkert. De afstudeerstage werd uitgevoerd in New York bij het Department of Microbiology van de Icahn School of Medicine at Mount Sinai, onder supervisie van dr. Gijs Versteeg en prof. dr. Adolfo García-Sastre. Daar werkte hij aan ISG15 (interferon-stimulated gene 15) van de muis. Direct na het behalen van zijn masterdiploma (*cum laude*) begon hij aan een promotietraject bij de LUMC-afdeling Medische Microbiologie, onder begeleiding van promotor prof. dr. Eric Snijder en zijn voormalige stagebegeleider dr. ir. Marjolein Kikkert. Zijn onderzoek richtte zich in eerste instantie op de interactie tussen het aangeboren immuunsysteem en virale replicatie en breidde zich gedurende het project uit naar de vorming van virusgeïnduceerde membraanstructuren onder begeleiding van dr. Montserrat Bárcena.

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