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Mechanisms of TRAIL-resistance

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Chapter 8

Nederlandse Samenvatting

Bibliography

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Publications

Nederlandse Samenvatting

TNF-gerelateerd apoptose-inducerend ligand (TRAIL) is in staat om in vitro tumorcellen te doden en gezonde cellen te sparen. Bovendien laten klinische studies zien dat patiënten het recombinant menselijke TRAIL (Dulanermin) goed kunnen verdragen. Al met al, maken de veiligheid van de behandeling en de gerichte apoptose van tumorcellen het oplosbare TRAIL-eiwit tot een veelbelovend geneesmiddel.

TRAIL behoort tot de TNF superfamilie en is het enige cytokine, dat bindt aan twee verschillende celdood receptoren, DR4 en DR5. Binding van TRAIL activeert de vorming van DISC, wat leidt tot caspase-afhankelijke apoptose. Naast het induceren van deze apoptotische signaleringsroute, kan TRAIL de ook de niet-gangbare, interne, kinase route activeren via dezelfde celdood receptoren. Zo kunnen, als voorbeeld, celdood receptoren na binding van TRAIL andere eiwitten aantrekken, om een secundair complex te vormen in plaats van de DISC. Dit multi-eiwitcomplex initieert overlevings- of proliferatie signaleringsroutes. Het vermogen van TRAIL om ook overleving of proliferatie te induceren is een van de redenen waarom tumorcellen resistent kunnen worden tegen TRAIL. Bovendien is de aanwezigheid van celdood receptoren op het plasmamembraan essentieel voor het initiëren van apoptose. Bijvoorbeeld, celdood receptoren in autophagosomen kunnen zich gedragen als lokreceptoren, die binden aan TRAIL om vervolgens autophagie te induceren in borstkankercellen.

In dit proefschrift ontrafelden we moleculaire mechanismen, die de TRAIL-gevoeligheid in tumorcellen controleren, met behulp van DR4- en DR5-specifieke TRAIL-varianten (**hoofdstuk 2 en 3**). Bovendien gebruikten we gecombineerde behandelingen met epigenetische geneesmiddelen om TRAIL-resistentie in tumorcellen te overwinnen (**hoofdstuk 5 en 6**).

Post-translationele modificaties, zoals glycosylering, bleken te correleren met gevoeligheid voor TRAIL. In **hoofdstuk 2** gebruikten we agonistische receptor-specifieke TRAIL-varianten om de individuele bijdrage van elke celdood receptor afzonderlijk, DR4 en DR5, te ontleden. Daartoe is gekeken naar het effect van door FUT3 en FUT6-gemedieerde fucosylering op de activiteit van de afzonderlijke receptoren. We ontdekten dat COLO 205 cellen, die een hoog expressie niveau van FUT3 en FUT6 hebben, gevoelig zijn voor zowel DR4- als DR5-gemedieerde apoptose. DLD-1- en HCT 116 cellen, die een relatief laag expressie level van FUT3 of FUT6 vertonen, zijn echter alleen gevoelig voor DR4-gemedieerde apoptose. Daarom hebben we FUT3-, respectievelijk FUT6-overexpresserende cellijnen gegenereerd en hun gevoeligheid voor de TRAIL-varianten onderzocht. Uit onze gegevens blijkt dat de DR5-gevoeligheid volledig is hersteld in FUT3- of FUT6-overexpresserende cellen.

Verder hebben we onthuld dat fucosylering de vorming van DISC en activering van caspase-8 beïnvloedt. Interessant is ook dat DR5-gemedieerde apoptose wordt verhoogd door extern toevoegen van L-fucose.

Extracellulaire blaasjes (EV's) zijn belangrijk bij intercellulaire communicatie. EV's dragen de boodschappen, waaronder DNA's en eiwitten, van donorcellen en leveren de inhoud af aan de ontvangende cellen. In **hoofdstuk 3** hebben we eerst aangetoond dat geconditioneerd medium (CM) afkomstig van kankercellen, TRAIL-gemedieerde celdood remt. Bovendien hebben we alleen DR5, maar niet DR4 in CM waargenomen. Vervolgens genereerden we cellijnen, die lange of korte varianten van DR5 tot overexpressie brengen en bewezen dat beide varianten bijdragen aan het verminderde aantal apoptotische cellen veroorzaakt door TRAIL. Verder detecteerden we DR5, maar niet DR4 aan het oppervlak van EV's. Tot slot hebben we laten zien dat TRAIL gevoeligheid wordt verbeterd na het weg halen van EV's uit het medium.

Hier boven genoemde twee hoofdstukken bieden nieuwe inzichten in het begrijpen van TRAIL-resistentie fenomenen. Vervolgens richten we ons op het verbeteren van TRAIL-gevoeligheid met combinatie strategieën. Histonen zijn de centrale componenten van nucleosomen. Daarom geven we een overzicht van recente studies over de rol van post-translationele modificaties van histonen in **hoofdstuk 4.** We hebben ook strategieën samengevat voor combinatietherapie om TRAIL gevoeligheid te verbeteren door te interfereren met afwijkende histon modificaties met behulp van remmers.

Histon acetylering is een van de belangrijke modificaties. Dit dynamische proces wordt gereguleerd door histonacetyltransferases (HATs), histondeacetylases (HDACs) en bromodomein eiwitten. In **hoofdstuk 5** gebruikten we eerst verschillende HDAC-remmers om de veranderingen van TRAIL-gevoeligheid op darmkankercellen te onderzoeken. We ontdekten dat RGFP966, een HDAC3-specifieke remmer, of PCI34051, een HDAC8-specifieke remmer, de TRAIL-gevoeligheid grotendeels verbetert in combinatie met agonistische receptor specifieke TRAIL-varianten. Bovendien werden meer apoptotische cellen waargenomen na de behandeling met TRAIL-varianten in HDAC1, 2 of 3 down gereguleerde cellen. Tot slot hebben we bewezen dat RGFP966 en PCI34051 TRAIL-geïnduceerde apoptose ook in 3D-spheroïd modellen verbeteren.

Niet-kleincellig longcarcinoma (NSCLC) is goed voor ongeveer 85% van de gevallen van longkanker. Klinische studies tonen aan dat EGFR-TKIs (EGFR-tyrosine kinase-remmers) efficiënter therapieën zijn dan chemotherapie. Patiënten die behandeld worden met de eerste generatie EGFR-TKI, zoals erlotinib, kunnen echter gemakkelijk resistentie ontwikkelen. In **hoofdstuk 6** hebben we een nieuwe p300 en CBP-selectieve remmer, A485, en TRAIL

gecombineerd om dit probleem op te lossen. We toonden aan dat de A485-TRAIL combinatie synergistisch celdood verhoogt en het volume van 3D-spheroïden van EGFR-TKI resistente cellen vermindert. Verder hebben we bewezen dat A485 TRAIL-geïnduceerde apoptose vergroot via de caspase cascade. Deze verbeterde apoptose is te danken aan het verhogen van genexpressie van caspases, zoals CASP3, 7, 8 en 9. Samengevat, tonen we een succesvolle combinatie van A485 en TRAIL in EGFR-TKI-gevoelige en resistente NSCLC cellen.

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Publications

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