Les stratégies de lutte contre l’obésité

Pour conclure, ce travail de thèse a permis de mettre en lumière le rôle central joué par la raréfaction capillaire au sein du tissu adipeux à l'obésité dans la survenue des dysfonctions de ce tissu, mais aussi des troubles systémiques qui débouchent sur les pathologies associées à l'obésité. La réponse angiogénique insuffisante dans ce tissu à l'obésité semble être la résultante d'un puissant signal et microenvironnement angiostatique, induit par FoxOs et la TSP-1. Ceux-ci participent au développement de l'hypoxie et de la fibrose tissulaire conduisant à la dérégulation des fonctions endocrines du tissu adipeux et à la sécrétion soutenue des adipokines et adipocytokines pro-inflammatoires dans l'ensemble de l'organisme.

Pendant longtemps, des stratégies de lutte contre l'obésité ont tenté de cibler la microcirculation et l'angiogenèse du tissu adipeux en espérant que leurs inhibitions permettraient de réduire l'expansion du tissu adipeux. Nos travaux, ainsi que ceux d'autres chercheurs, démontrent que la seule stratégie thérapeutique ciblant la microcirculation adipeuse, valable pour contrecarrer l'obésité et ses pathologies associées, est de stimuler l'angiogenèse afin de lever le défaut angiogénique et la raréfaction capillaire, retrouvés dans les tissus adipeux chez l'obèse. Dans cette perspective thérapeutique, la pratique régulière de l'exercice physique semble être le choix le plus en adéquation pour combattre les troubles physiologiques impactant le tissu adipeux à l'obésité. En effet, en plus d'induire la lipolyse et la perte de poids, notre recherche a mis en évidence la capacité de l'exercice à stimuler l'angiogenèse du tissu adipeux chez l'obèse et de restaurer l'homéostasie vasculaire, ainsi que les fonctions endocrine et métabolique de ce tissu. Ce travail montre pour la première fois que cette action pro-angiogénique de l'exercice serait moléculairement provoquée par une augmentation de Mdm2, permettant de lever le frein angiostatique exercé par FoxOs et la TSP-1 et d'activer le VEGF-A.

Ces résultats apportent donc une approche nouvelle dans la compréhension des effets bénéfiques de l'exercice sur la santé de l'individu obèse. En pleine époque de sédentarisation des sociétés, ces données doivent encourager les patients et les professionnels de santé à privilégier, de façon naturelle, la pratique d'une activité physique adaptée et régulière. Nos résultats s'ajoutent à de nombreuses autres preuves biologiques sur l'efficacité de l'exercice comme élément thérapeutique, avec une efficacité au moins importante que celle des thérapies moléculaires. La recherche de nouveaux composés, capable de mimer les effets biologiques de l'exercice est d'ailleurs en plein essor. Au cours des dernières années, ont émergé des molécules comme l'AICAR (activateur AMP-kinase) ou le GW501516 (agoniste de PPAR δ), capable de stimuler l'activation et réduire la fatigue des fibres musculaires afin d'améliorer l'endurance

(Narkar *et al.* 2008; Pokrywka *et al.* 2014). Nos conclusions offrent également des nouvelles perspectives de recherche en biomédecine. La découverte de composés naturels ou pharmacologique, capables de provoquer l'augmentation de Mdm2 ou la dégradation de FoxOs au niveau endothéliale dans le tissu adipeux, permettrait de lutter contre les troubles de l'homéostasie vasculaire chez les patients obèses et de réduire le risque de survenue de pathologies cardiométaboliques.

Avant d'envisager de tels traitements, la validation de nos travaux et la confirmation de l'implication de l'axe Mdm2-FoxOs dans la régulation de cette réponse pro-angiogénique du tissu adipeux à l'exercice sont nécessaires. Pour cela, l'utilisation de modèle transgénique ciblant cette voie au niveau endothéliale semble indispensable. Il s'avère en effet que les modèles transgéniques de souris obèses, mimant les effets de l'exercice sur l'expression des facteurs VEGF-A (surexpression) et TSP-1 (sous-expression) au niveau des tissus adipeux blancs et bruns, présentent les mêmes améliorations des fonctions adipeuses et des paramètres métaboliques systémiques que nos souris HFS entrainées (Elias *et al.* 2012; Inoue *et al.* 2013; Kong *et al.* 2013; Sung *et al.* 2013; Shimizu *et al.* 2014). Ces résultats montrent les rôles majeurs de la balance angiogénique VEGF-A/TSP-1 et de la stimulation de l'angiogenèse dans le tissu adipeux par l'exercice physique sur la santé globale de l'individu obèse.

La délétion de FoxO1 et 3α, spécifiquement au niveau de l'endothélium, a mis en évidence l'importance de ces facteurs de transcription dans l'établissement d'un microenvironnement anti-angiogénique, pro-inflammatoire et la survenue de l'insulino-résistance dans le muscle squelettique à l'obésité (Nwadozi *et al.* 2016). Les effets d'une telle délétion n'ont en revanche pas été décrits au sein du tissu adipeux chez la souris obèse. Les conséquences d'une modulation induite de l'expression de Mdm2 sur la vascularisation du tissu adipeux n'ont également jamais été étudiées. Une étude menée chez des souris hypomorphes pour Mdm2 a permis de démontrer le rôle de régulateur de cette protéine dans la réponse pro-angiogénique du muscle à l'exercice. En effet, ces souris ne présentaient plus d'augmentation de la densité vasculaire après un protocole d'entrainement. La stimulation de l'expression du VEGF-A dans le muscle à l'exercice est également abolie chez ces souris, où il a également été retrouvé un haut niveau d'expression pour les protéines FoxO1 et TSP-1 (Roudier *et al.*, 2012). L'étude de la balance angio-adaptative du tissu adipeux chez ces souris hypomorphes, soumis à notre protocole d'exercice volontaire, permettrait assurément de valider ou d'invalider notre hypothèse de recherche. L'action régulatrice de Mdm2 sur p53 et son rôle pro-tumorale ont conduit à de nombreuses recherches en cancérologie pour concevoir des inhibiteurs

pharmacologiques de Mdm2 (Vassilev 2007; Burgess *et al.* 2016). Si des inhibiteurs de l'interaction Mdm2-p53 et Mdm2-HIF-1α existent (Zhao *et al.* 2015; Burgess *et al.* 2016), aucune molécule capable de réduire l'interaction entre Mdm2 et FoxO1 n'a été identifiée. Néanmoins, l'administration d'inhibiteur de l'expression de Mdm2, comme les oligonucléotides MBO (*mixed-backbone oligonucleotides*) (Zhang *et al.* 2005), chez nos souris HFS entrainées permettrait de visualiser l'abolition éventuelle des effets bénéfiques de l'exercice sur la microcirculation du tissu adipeux et ainsi confirmer notre hypothèse.

Très vraisemblablement du fait de son rôle oncogène, aucune investigation n'a conduit au développement de substances ou de molécules en mesure de stimuler l'expression et la stabilisation de Mdm2. Réussir à induire une surexpression génétique ou pharmacologique de Mdm2 au niveau de la cellule endothéliale du tissu adipeux pourrait conduire à mimer les effets bénéfiques de l'exercice physique sur la santé de l'individu obèse. Cela pourrait constituer une perspective thérapeutique de premier choix, plus particulièrement chez les patients atteints d'une obésité très sévère, pour qui la pratique d'une activité physique s'avère être une stratégie thérapeutique difficile à mettre en place.

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