V. Conclusions et perspectives

Ce travail s'inspire des connaissances et de l'expertise acquises par notre laboratoire dans le domaine de la biologie des tissus conjonctifs. L'ADAMTS2 est une métalloprotéase requise pour la maturation des collagènes fibrillaires, expliquant son importance dans l'élaboration et le maintien de la trame fibrillaire de support et des structures conjonctives dans leur ensemble. L'objectif de nos études était de caractériser de manière plus précise le rôle de l'ADAMTS2 dans des processus physiologiques et pathologiques, et d'en déduire d'éventuelles applications en thérapeutique clinique.

Nous avons confirmé que l'ADAMTS2 détenait une fonction essentielle au cours de l'embryogenèse et du développement, notamment par son rôle majeur dans la maturation des procollagènes fibrillaires de type I et de type III dans la peau et le poumon. Son activité spécifique a également été mise en perspective avec celle des deux autres aminoprocollagène peptidases, les ADAMTS3 et 14.

L'impact de l'inhibition de l'ADAMTS2 au cours de la formation pathologique de tissu fibreux cicatriciel a été démontré dans des modèles murins de fibrose hépatique et de réaction granulomateuse à corps étranger. A ce titre, l'ADAMTS2 apparaît comme une cible thérapeutique d'intérêt pour le traitement de toute affection caractérisée par le dépôt d'une trame cicatricielle excessive, dont la fibrose hépatique.

Enfin, le potentiel anti-angiogène de l'ADAMTS2 a été démontré à la fois *in vitro* et *in vivo*. Son efficacité remarquable résulte de son action au cours de plusieurs étapes distinctes de la formation des néo-vaisseaux. Les mécanismes moléculaires précis par lesquels l'ADAMTS2 agit sur les cellules endothéliales et l'inhibition de la croissance tumorale restent à préciser.

De nombreuses questions restent ouvertes et seront abordées selon plusieurs approches complémentaires.

- D'autres substrats potentiels de l'ADAMTS2 seront recherchés par des techniques de protéomique différentielle.
- Le récepteur et les mécanismes intracellulaires utilisés par l'ADAMTS2 pour moduler les propriétés des cellules endothéliales seront identifiés. Ces travaux permettront de déterminer si l'ADAMTS2, certains de ses domaines, ou éventuellement des molécules

régulatrices des voies de signalisation impliquées, ont un avenir thérapeutique en tant qu'inhibiteurs de l'angiogenèse.

- Des inhibiteurs de l'activité ADAMTS2 doivent être développés et évalués pour leur potentiel anti-fibrotique dans divers modèles animaux. Plusieurs possibilités existent, que ce soit sous la forme d'acides nucléiques (ARN interférentiels), d'inhibiteurs synthétiques ou physiologiques ou d'anticorps bloquants. De tels inhibiteurs pourraient également être développés pour les ADAMTS3 et 14.
- Enfin, des souris déficientes pour les ADAMTS3 et 14 sont en cours de création. Si elles sont viables, elles permettront d'évaluer l'impact direct l'absence de ces deux enzymes *in vivo* et de préciser d'éventuelles redondances fonctionnelles entre elles et avec l'ADAMTS2. En cas de problème de viabilité ou fertilité, une approche par invalidation conditionnelle sera entreprise.

VI. Bibliographie

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