

<http://hdl.handle.net/1765/106448>



Summary

The first research question that contributes to the main aim of the thesis was: *How are macrophages of different phenotypes involved in inflammatory tissue degeneration and degenerative joint diseases?* This question was mainly addressed in **chapters 2 to 5** (Figure 9.1). In this thesis, a distinction between three main phenotypes was made: pro-inflammatory, anti-inflammatory, and tissue repair macrophages, of which their *in vitro* counterparts were defined as: M(IFN γ +TNF α), M(IL-10), and M(IL-4), respectively (**chapters 2, 3, 5**). Our first step towards answering the question was revealed in **chapter 3**, where it was found that pro-inflammatory macrophages exacerbated cartilage degeneration by increasing production of NO, increasing release of GAGs, and stimulation of cartilage matrix degrading enzymes and inflammatory proteins (Figure 9.1, bottom left). In our next step, we investigated which phenotypes of macrophages were mainly present in the synovial tissue of end-stage OA patients. It was seen that the tissue repair macrophages were the predominant phenotype present in the synovium of these patients (**chapter 2**). We could also speculate that chemokines, and in particular expression of *CCL2*, are involved in facilitating monocyte recruitment into synovium followed by polarization into anti-inflammatory and tissue repair macrophages (Figure 9.1, upper right, dashed lines). Finally, to see the whole picture, we mapped the presence of three macrophage phenotypes during the course of OA *in vivo* (**chapter 4**) and it was found that anti-inflammatory macrophages appear early after OA onset, while pro-inflammatory and tissue repair macrophages appear in mid to late stage OA (Figure 9.1, middle).

The second research question of this thesis was: *How can modulation of macrophage phenotypes be applied to control either inflammation or their response to biomaterials?* This question was mainly addressed in **chapters 4 to 7**. **Chapter 5** revealed that common medications (corticosteroids, rapamycin, BMP-7, and pravastatin) were able to direct synovial inflammation *in situ* by effecting specific macrophage phenotypes (Figure 9.1, bottom). Modulation of the synovium by a corticosteroid also had a positive functional effect on cartilage explant degeneration by inhibiting matrix degrading proteins and inhibition of chondrocyte hypertrophy, likely due to enhancing the performance of tissue repair macrophages (**appendix chapter 5**). Moreover, **chapter 4** revealed that the three macrophage phenotypes are also likely to have specific functions *in vivo* by suppressing osteophyte formation and synovial inflammation (Figure 9.1, bottom right). An inflamed tissue environment may impede biomaterial-based joint reconstruction and regeneration. It was found that monocytes are likely to polarize towards pro-inflammatory macrophages in response to biomaterials which was even aggravated by obesity (Figure 9.1, upper left). Finally, with the idea to be able to intervene these processes, we have shown as proof of concept that the behavior of the macrophages in response to a biomaterial can also be modulated by drugs (Figure 9.1, middle).

CONCLUDING REMARKS

To conclude, the work described in this thesis revealed that pro-inflammatory, anti-inflammatory, and tissue repair macrophages each have their own behavior and association with OA development and progression. The studies in this thesis present methods on specifically modulating a macrophage phenotype within tissue with the ultimate goal: suppressing OA progression. These methods can be interpreted as guidelines for selecting the most suitable approach for modulation while taking into account the stage of the disease, the inflammatory state of the tissue, or the type of biomaterial in case of biomaterial-based joint tissue regeneration. The knowledge can be applied to use macrophage phenotype modulation as a tool to intervene or suppress processes that contribute to degeneration of joint tissues.

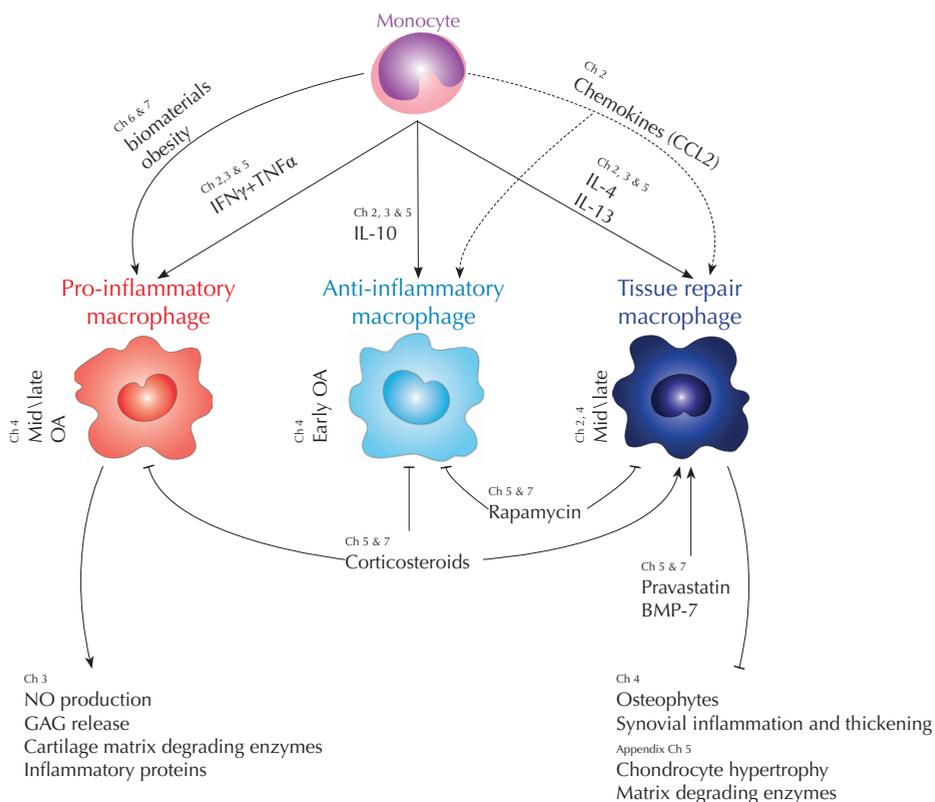


Figure 9.1: Thesis summary on macrophage phenotypes and their role in degenerative joint disease. Solid lines represent associations revealed in each chapter, while dashed lines represent indicative links.