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Genes and mediators of inflammation and development in osteoarthritis

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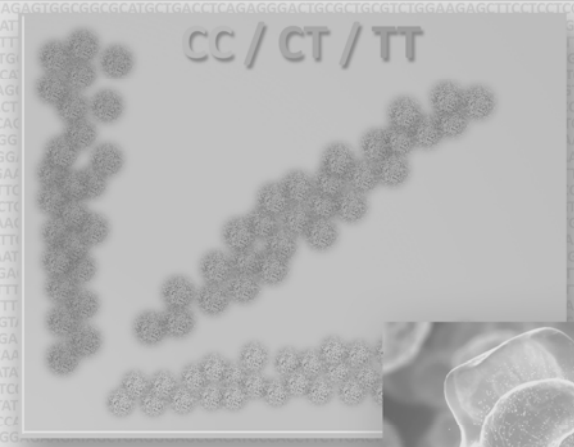

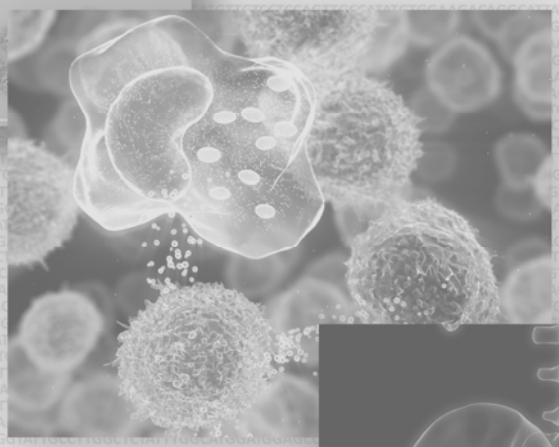

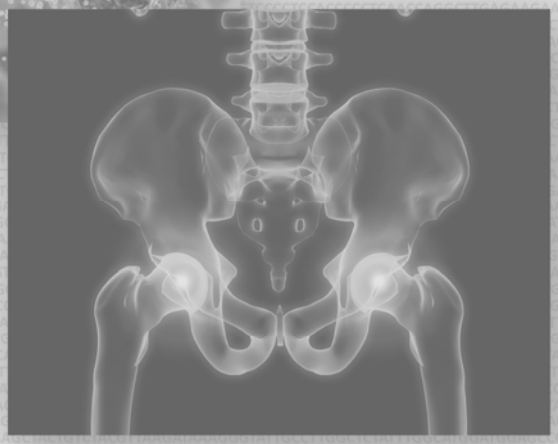

Summary

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We have investigated associations of levels of inflammatory mediators, genetic variation and features of osteoarthritis (OA). A summary of our findings is provided in Table 1. Overall, we were only able to find fitting associations for the *CRP* gene. We identified a haplotype of the *CRP* gene which associated to higher circulating levels of serum HsCRP as well as to increased numbers of affected joints of the hand in the GARP study (Chapter 2.3), which follows the generally accepted hypothesis that a high inflammatory status is detrimental to the cartilage. The association is most likely reflecting a causal relation between high basal CRP levels and the onset of hand OA. It is contradictory that in spite of the identified association the levels of the GARP subjects with high amounts of hand OA are not different from the other GARP participants, possibly due to the fact that all participants in this study are affected by OA at multiple joint sites.

A more complex association and interaction described in this thesis regards the haplotypes of the IL-1 gene cluster which previously were shown to be associated with the innate levels of cytokines and OA features thereby verifying the generally accepted hypothesis that high innate IL-1β production capacity is detrimental to the cartilage. However, as described in this thesis we identified a haplotype associated to innate lower IL-1β bio-availability which was also associated to subjects with the highest overall ROA scores, indicative of more complex mechanisms underlying the associations found (Chapter 2.1).

Furthermore, for the *SELS* gene we found evidence for a role of Selenoprotein S genetic variation in the circulating levels of components representing pro- and anti-inflammatory signaling in GARP subjects. In spite of these associations to cytokine levels we were unable to show that these genetic variations associated to OA features, whereas we did observe association of a third component mainly representing chemokine variation to features of hand OA and degeneration of the spinal discs (Chapter 2.4).

In these analyses for each answer found, we raised new questions towards the role of genetic variation of genes encoding regulators of the immune system. In search of new loci associated to innate immunity and thereby possibly involved in OA etiology, we showed the association of *CD53* to innate TNF alpha levels, however, the innate levels of TNF alpha appear to have no substantial role in OA etiology. As we expected based on this knowledge, the *CD53* genetic variation which was associated to TNF alpha did not show associations to OA or any subtypes thereof (Chapter 2.2).

Table 1. Summary of associations between genetic variation, inflammatory mediators and OA.

	Associations		
Gene	**Haplotypes to levels**	**Haplotypes to OA**	**Levels to OA**
CRP	**Yes** (Serum HsCRP)	**Yes** (Hand ROA)	**No**
IL-1 gene cluster	**Yes** (Innate IL-1β bio-availability)	**Yes** (ROA)	**Yes** (Innate IL-1β bio-availability)*
SELS	**Yes** (Cytokines and serum HsCRP)	**No**	**Yes** (Chemokines)

* Innate IL-1β bio-availability hold an inverse relation for haplotype association and levels association to OA, i.e. the associated haplotype mediates lower Innate IL-1β bio-availability whereas the associated levels appears to be high innate IL-1β bio-availability

Aided by the various genetic findings in the OA research, including larger genome wide approaches, the developing view in the OA research field is that in addition to the long investigated inflammatory genes there is mounting evidence that genetic variation at genes involved in the processes of skeletal development and maintenance, and the endochondral

ossification in particular may contribute to the heritabile component of OA. The identification of *DIO2* genetic variation which associated to OA in a large, multicenter and multiethnic study triggered us to investigate the coding polymorphism rs225014. By use of a differential allelic expression assay we showed that the risk allele is transcribed at a higher rate in the affected cartilage of heterozygous carriers of this polymorphism (Chapter 3). This leads us to hypothesize that a *cis* acting regulatory element, such as a differential methylation or promoter polymorphism may underlie the *DIO2* association to OA. These data are corroborated by the immunohistochemical analyses of OA and non OA cartilage, where we show higher protein presence of *DIO2*'s gene product type II deiodinase (D2), as well as for the other thyroid signaling related proteins type III deiodinase and thyroid receptor beta (Chapter 3). Through a higher protein presence of D2 which may be at least in part caused by the higher activity of the risk polymorphism, the inactive thyroid hormone T_4 is converted to active thyroid hormone T_3. During the endochondral ossification, D2 activity increases T_3 levels in the growth plate, and this hormone triggers the chondrocytes to enter their terminal differentiation, ultimately forming the bone and facilitating the longitudinal growth of bones. This process has a striking resemblance to the processes observed in the articular cartilage where the chondrocytes display similar features. Through the identification of *DIO2* genetic variation associated to OA, we may have found additional proof that a loosening of the maturational arrest of chondrocytes during life may be lost, ultimately leading to the loss of articular cartilage and formation of osteophytes.