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**Sox5 and chromatophores: Switching pigment cell fates**

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Unlike mammals and birds, certain fish species possess more than one type of neural crest-derived pigment cells. Zebrafish and medaka, among others, harbour chromatophores, which include black melanophores, iridescent iridophores and yellow xanthophores. Furthermore, the medaka bears a distinct chromophore population called leucophores. While the specification of melanophores and iridophores from a common progenitor has been linked to the expression of Mitf and FoxD3 respectively (Curran et al. 2009; Curran et al. 2010), the leucophores’ origin and differentiation process remain poorly understood. Previous studies have suggested a close relationship between xanthophores and leucophores based on their shared biochemical properties, but never linked them developmentally (Braasch et al. 2007). Nagao et al., through the molecular characterization of several spontaneous mutants harbouring defects in xanthophore and leucophore numbers, shed light on the transcription factor Sox5 as a critical developmental switch in their respective differentiation.

First, Nagao and colleagues determined that the *ml*-3 locus encodes a factor switching specifically the fate of xanthophores in favour of leucophores in a dose-dependent fashion without altering melanocyte or iridophore populations. These data highlight the presence of a common progenitor cell for these two lineages. Using positional cloning, the authors then linked the *ml*-3 locus to the transcription factor Sox5, a gene previously described to harbour the capacity to modulate the activity of several members of the SoxE transcription factor family, including Sox10, a critical player of neural crest and pigment cell development (Stolt et al. 2008; Harris et al. 2013). Nagao et al. identified the *ml*-3 mutation as resulting from an aberrant splicing of exon7, which triggers a premature STOP codon and truncation of Sox5 prior to its HMG box and 2nd coiled-coil domain. Gene silencing using morpholinos and independent mutagenesis both led to increased leucophore numbers and absence of xanthophore without affecting other pigment cells, further validating Sox5 loss of function as responsible for the *ml*-3 phenotype.

The authors were then able to show, with the help of cell transplantation experiments between *ml*-3 and control embryos and vice versa, that cells originating from Sox5-deficient embryos fail to give rise to any significant number of xanthophores. In contrast, control cells were able to generate normal numbers of xanthophores in *ml*-3 mutant fishes. Furthermore, they demonstrated an aberrant increase in leucophore numbers in embryos lacking Sox5. However, the observed changes in pigment cell subpopulations, were not only due to cell-autonomous effects of *sox5* deficiency, but also caused by the lack of xanthophores allowing leucophores to ectopically populate chromatophore free territories. Hence, Nagao et al. show that Sox5 acts as fate switch in pigment cell lineages, but the cell numbers constituting these lineages are apparently controlled independently from Sox5.

Finally, a phenotypic comparison of *lf-2* (*pax7a*) mutants, which lack both xanthophores and leucophores (Kimura et al. 2014), with *ml*-3 mutant embryos enabled the authors to identify a genetic cascade resulting in the specification of both of the above mentioned lineages. Using detailed embryonic in situ hybridization expression analysis, Nagao et al. described how Sox5 expression in *ml*-3 is
maintained in the embryonic neural tube and in neural crest derivatives in the medial pathway, but not in areas associated with xanthophores, further underlining the lineage-specific Sox5 dependency of xanthophores. Similar experiments in pax7a-deficient embryos revealed the same lack of Sox5-expressing cells in the lateral trunk region. Together with the phenotypic data of If-2/ml-3 double mutant showing no difference from the single If-2 mutant phenotype, the authors show that Pax7a is required for the generation of a common progenitor for xanthophores and leucophores and is genetically upstream of sox5. However, the Sox5 expression status in this progenitor cell population is unclear. Indeed, the in situ hybridization analysis presented by the authors reveals a relatively broad expression of Sox5 in pre-migratory neural crest cells. Thus, two scenarios are possible: a repression of Sox5 upon leucophore differentiation from a Sox5(+) progenitor population, where Sox5 is not critical for the survival of the latter; or a de novo expression of Sox5 upon xanthophore differentiation from a Sox5(-) progenitor population. In any case, the data indicate that Sox5 expression levels must be tightly regulated during pigment cell development, although the factors acting upstream of Sox5 have not yet been identified. The position of Sox5 as critical switch between xanthophore and leucophore fates also suggests that Sox5 gain of function would prevent the generation of leucophores to the benefit of xanthophore derivatives, but this remains to be demonstrated. Additionally, it would be of interest to address whether functional manipulation of Sox5 or of a related factor would be sufficient to induce emergence of leucophores in Zebrafish, which normally lack this pigment cell lineage but have xanthophores.

In summary, Nagao et al. have identified Sox5 as a fate switch in the differentiation process between the xanthophore and leucophore cell population from a Pax7a-dependent common progenitor, in Medaka. Although the authors propose an interaction model involving Sox10 and Pax7a and resulting in a modulation of their respective targets, the precise modus operandi of Sox5 in the differentiation of xanthophores by target gene-specific regulation has yet to be characterized. Their data strengthen the biological importance of Sox5 as a central genetic regulator, not only in fish, but perhaps also in mammalian pigment cells as previously suggested by Stolt et al. (Stolt et al. 2008). Moreover, this study provides another intriguing example of how differential expression of Sox proteins controls fate decision processes during neural crest development (John et al. 2011).


Kimura, T. et al., 2014. Leucophores are similar to xanthophores in their specification and differentiation processes in medaka. *Proceedings of the National Academy of Sciences of the United States of America*.