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APPENDIX 2

T is for Thalidomide

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From 1959 until its withdrawal from the market in 1961, after alarming reports by Mc Bride and Lenz,[1,2] the administration of thalidomide as a sedative caused several thousands of cases of congenital malformations. Although the mechanism underlying the etiology of these iatrogenic deformities has been studied by many, an explanation for thalidomide's teratogenic effect on the human embryo has remained elusive for almost four decades now. The renewed interest for the pharmacological action of the drug thalidomide as an immunomodulatory agent in diseases such as erythema nodosum leprosum,[3] diverse ulcerative disorders,[4-6] reumatoid arthritis[7] and graft-versus-host disease,[8] only intensifies the need to understand its mechanism of action. Here we would like to use the strong similarities between thalidomide embryopathy and two human syndromes, the Holt-Oram and ulnar-mammary syndrome, to come to a genetic explanation for the complicated phenotype observed in thalidomide deformities.

In 1986, Newman pointed out the similarities between the embryopathy caused by administration of thalidomide and a genetic syndrome: "In Holt-Oram syndrome,..., the upper limb reduction pattern is very similar to that of thalidomide, although the legs are unaffected".[9] Indeed, a striking resemblance exists between the phenotypes of many of the thalidomide victims and patients with Holt-Oram syndrome[9] (OMIM 142900) (see figure 1), both show identical severe upper limb deficiencies and cardiac septation defects. In both cases one finds the same thumb abnormalities (triphalangism, hypoplasia and aplasia), and severe aplasia of the forelimb long bones, with aplasia of the forearm most prominent on the radial side (radial aplasia).

![Figure 1](From Newman, C.G.H: teratogen update. Teratology, 32:133, 1985, with permission of Wiley-Liss, Inc.)
However, patients with Holt-Oram syndrome do not show any deformities of the lower limb, and thus the similarity between both conditions has received little further attention.

Another genetic syndrome which shares some of the features of thalidomide embryopathy is the ulnar-mammary syndrome (OMIM 181450).\(^\text{10}\) both syndromes have in common the same defects in tooth (hypoplasia), renal (agenesis/hypoplasia), genital, anal (atresia/stenosis) and pyloric (atresia/stenosis) development.

Interestingly, the genetic defects underlying the cause of both the Holt-Oram and the ulnar-mammary syndrome have now been identified.\(^\text{11-13}\) this gives a surprising new insight in the possible correlation between the phenotypes observed in these genetic syndromes and those in children with thalidomide deformities. Holt-Oram syndrome is caused by mutations in the gene encoding the human transcription factor TBX-5, whereas the ulnar-mammary syndrome is caused by mutations in TBX-3. Both are members of the T-box family of transcription factors, originally identified in the mouse.\(^\text{14-15}\) Members of the T-box gene family share a DNA-binding domain, the so-called T-box. Interestingly, where TBX-5 plays a critical role in the development of the upper limb and heart, a highly homologous T-box family member, TBX-4, specifies the development of the lower limb.\(^\text{16-17}\) Thus it is tempting to postulate that thalidomide or one of its many metabolites\(^\text{18}\) negatively interferes with either the function of the T-box domain or with a common mechanism whereby those T-box containing transcription factors are activated.

The most pronounced effect of thalidomide is disturbance of limb development. Interference with the action of T-box transcription factors would fit well within the framework of our current understanding of this complex process.\(^\text{19}\) Both thalidomide exposure and Holt-Oram syndrome lead to the same loss of proximal limb structures specifically. In the development of the vertebrate limb, the proximal-distal axis is established by the specialised epithelium at the tip of the outgrowing limb bud, in an area called the apical ectodermal ridge (AER), which secretes and can be replaced by FGF. At the outset, the developing limb mesenchyme is only able to generate proximal limb structures. However, the FGF produced by the AER re-specifies the cell fate of some of the cells with a high proliferation rate underlying the AER, called the progress zone, to form distal structures. Tabin proposed that as thalidomide blocks proliferation in the progress zone and the limb bud fails to lengthen, all cells in the developing limb are exposed to the FGF still produced by the AER, and are therefore distalised.\(^\text{20}\) The FGF specifies a distal cell fate in these cells and as a result a limb develops in which the lack of proximal elements is especially pronounced, whereas distal elements may still be present (figure 2).

Since Holt-Oram syndrome shows the same defects in limb development, this hypothesis also applies to this syndrome. Importantly, identification of
the genetic defect in Holt-Oram syndrome has now shown that the lack of proliferation of the limb bud mesenchyme in this syndrome is caused by impaired action of TBX-5. The identical features in thalidomide-affected embryo’s can thus be explained by the same mechanism.

This is an attractive and unifying hypothesis because this mechanism of action is easily extrapolated to account for other features of the very complex “thalidomide phenotype” and more importantly may also explain some of the anti-inflammatory actions of thalidomide. An identical interference with the action of TBX-4 can account for the observed lower limb abnormalities and analysis of the ulnar-mammary syndrome shows that inhibition of transcriptional activity of TBX-3 can explain many of the deformities of the inter-

Figure 2. (A) Normal situation. Initially all cells in the limb bud mesenchyme have a proximal cell fate. The FGF from the AER forms a concentration gradient that distalises the fate of the rapidly proliferating cells in the progress zone. In our model the proliferation of the mesenchyme depends on TBX-5 mediated transcription of T-box target genes. (B) Holt-Oram syndrome/thalidomide embryopathy. Defective TBX-5 mediated transcription interferes with proliferation of the limb bud mesenchyme. As a result, the limb bud fails to lengthen, however the AER continues to secrete FGF. All cells in the limb bud are now exposed to a high concentration of FGF, thus most of limb is distalised, resulting in the deformities observed in both Holt-Oram syndrome and thalidomide embryopathy.
nal organs. At the time we became aware of the similarity between the thalidomide phenotype and syndromes caused by mutations in T-box factors we were unable to account for the anti-inflammatory effects of thalidomide. Recently however one of the T-box family members, T-bet has been shown to be the critical transcription factor in the development of a T-helper 1 type immune response and the production of IFN-gamma and interleukin-12 by these cells.\textsuperscript{21, 22}

In conclusion, we propose that thalidomide interferes with T-box family member mediated transcription. We suggest a T-box family specific, but not a single T-box gene selective activity of the drug. This interference could account for the upper and lower limb deformities, cardiac septal wall defects and many of the other internal organ abnormalities, observed in children affected by the thalidomide syndrome.
Appendix 2

References


