Binding Site Cooperativity and Dual Signal Integration in CYP1A1 Induction

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CYP1A expression in liver



Braeuning, A. & Schwarz, M. Biol. Chem. 391, 139–148 (2010) Braeuning, A., Köhle, C., Buchmann, A. & Schwarz, M. Toxicol. Sci. 122, 16–25 (2011).

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CYP1A

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1D data





1D data shows cooperativity of binding sites





promoter logic



promoter logic



promoter logic



promoter logic



strongest binding sites



strongest binding sites recruit RNA Polymerase



strongest binding sites recruit RNA Polymerase

B site most important cooperation partner



strongest binding sites recruit RNA Polymerase

B site most important cooperation partner

CYP1A1 expression modulated by B-catenin & TCDD



Braeuning, A., Köhle, C., Buchmann, A. & Schwarz, M. Toxicol. Sci. 122, 16–25 (2011).

AhR expression not modulated by ß-catenin & TCDD



Braeuning, A., Köhle, C., Buchmann, A. & Schwarz, M. Toxicol. Sci. 122, 16–25 (2011).





2D data shows interplay of B-catenin & TCDD





PL model unable to describe B-catenin integration





PL model unable to describe B-catenin integration





promoter logic

Modeling approach – adding TF formation



transcription factor formation +

promoter logic

PL + TFF model capture dual signal integration



Conclusions

Cooperativity of CYP1A1 promoter binding sites

Dual signal integration on CYP1A1 promoter

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- Cooperativity of CYP1A1 promoter binding sites
 - 2 strongest binding sites control recruitment of RNAP
 - second DRE is most important cooperation partner
- Dual signal integration on CYP1A1 promoter

Conclusions

- Cooperativity of CYP1A1 promoter binding sites
 - 2 strongest binding sites control recruitment of RNAP
 - second DRE is most important cooperation partner
- Dual signal integration on CYP1A1 promoter
 - simple promoter logic not sufficient to capture effect of B-catenin on CYP1A1 expression
 - additional transcription factor formation necessary
 - combined models capture dual signal integration

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