CDB SEMINAR

Speaker: Michael Karin

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Title: "IKKα and the Control of Epidermal Differentiation"

Date:	Friday, July 15
Time:	11:00 A.M.～12:00 P.M.
Place:	1F Auditorium of Building C, CDB

Summary:

IKKα is one of two catalytic subunits of the IκB kinase (IKK) complex. Gene disruption experiments reveal that IKKα plays a critical role in development of the mammalian epidermis and skeletal morphogenesis. Yet, IKKα was found to have only a minor role in activation of NF-κB in response to conventional proinflammatory and innate immune stimuli. In fact, recent work has shown that IKKα plays a negative regulatory role in the NF-κB activation response by limiting the residence of NF-κB dimers at promoters of NF-κB target genes. Importantly, however, the critical role of IKKα in the control of epidermal differentiation was found to be independent of its protein kinase activity and unrelated to the regulation of NF-κB activity. Further analysis has shown that while the protein kinase activity of IKKα is exerted in the cytoplasm, its role in induction of terminal keratinocyte differentiation was found to depend on its translocation to the nucleus. Furthermore, we have shown that the effect of IKKα on skeletal morphogenesis is indirect and is exerted through its key role in keratinocyte differentiation. In the absence of IKKα, keratinocytes fail to undergo terminal differentiation and as a result overproduce members of the FGF family, which in turn negatively regulate BMP signaling in the mesoderm. These results provide a clear demonstration that the ectoderm, where keratinocytes reside, has a key role in controlling the morphogenesis of mesodermal derivatives.

In trying to understand how IKKα functions in the nucleus to control epidermal differentiation, we searched for transcriptional targets for IKKα in keratinocytes. I will describe the results of this recent analysis, which point out a key role for IKKα as a transcriptional co-activator in the BMP/TGFβ signaling pathway. We also searched for upstream regulators of IKKα expression during epidermal differentiation and, in collaboration with the groups of Antonio Constanzo and Dennis Roop, identified IKKα as a critical target for the p63 transcription factor.

Host **Masahiko Hibi** Vertebrate Axis Formation, CDB
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