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GATA4 represses ERBB2 expression in cancer cells : a new tumor suppressor?

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Overexpression of the receptor tyrosine kinase ERBB2 observed in 20-30% of breast cancers is a poor prognosis indicator associated with resistance to chemotherapy. We have shown that a negative feedback regulatory loop associates the tyrosine kinase receptor ERBB2 and the transcription factor GATA4 in breast cancer cells[1]. At least six transcription factors (CSDA/ZONAB, FOXP3, GATA4, MYB, PAX2, PEA3) acting as transcriptional repressors of the *ERBB2* gene have been described so far. We have recently proposed that *ERBB2* gene amplification is used to overcome repression of its expression by sequence-specific transcription factors[2]. In parallel, nuclear translocation of some RTKs has been previously described. Hence, ERBB2 and 2 other members of the EGFR family were reported to translocate in the nucleus, to bind to gene promoters and to activate or repress the transcription of specific genes. Although the mechanism how intact receptors extricate themselves from the plasma membrane remains unclear. For ERBB2, a nuclear translocation process involving endocytosis, endosomal sorting, importin β and nuclear pore complex protein has been proposed. This gene encodes 2 major isoforms (ERBB2a and b). ERBB2b lacks a signal peptide and can located in the nucleus. Humanized monoclonal antibodies targeting the membrane-anchored form of ERBB2 are a major anti-cancer therapy in ERBB2+ patients. Nevertheless, resistance to treatment is often observed. Whether the nuclear form of ERBB2b is a cause of this resistance remains to be demonstrated.

Biography

Jean Imbert completed a Ph.D. at Université de la Méditerranée (Marseille) and postdoctoral studies at NHI/NCI (Bethesda, MD). He co-headed the laboratory of Molecular and Functional Immunology before establishing his own research group in 1996 at Inserm U119. In 2007, he moved to the campus of Marseille-Luminy where he leads the research group of Transcriptional Regulations and the platform Transcriptomics and Genomics Marseille-Luminy (TGML). He is currently studying the transcriptional regulatory networks involved in various cancers. He has contributed more than 70 peer reviewed international journals in the field and provided more than 100 lectures in France and abroad.