Bistable molecular switches in human protein-protein interaction

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Aberrations in cancer genome might cause the changes of biological systems to obtain robustness against environmental perturbations. Cancer biological systems entails inherent trade-offs between robustness and fragility. Intensive attack to fragile sites of cancer biological systems might introduce a new paradigm into the treatment of cancer (1).

Multistability and oscillations is the main dynamic properties of gene-regulatory circuits which may represent the status of biological systems. Theoretically, multistability can be achieved by feedback loops with even-numbered negative interactions (2) and it have been found in the bacterophage λ switch (3) and *Escherichia coli* (4).

We defined the possible bistable molecular switches as Fig. 1A based on the theoretical study for modeling genetic switches with positive feedback loops (5). A social network analysis software "Arabesque" extracted 40 type1 switch pairs, 49 type 2 switch pairs and 2414 type 3 switch pairs from human protein-protein interaction database (ResNet 3.0 by Ariadne Genomics Inc.). Some switch pairs demonstrated that conversion of switch ON/OFF patterns occurred when compared mRNA expression of medulloblastoma cell lines (DAOY, OWS76, TE671 and UW426) with that of normal cerebellum. For example, Fig. 1B demonstrated FGF2-PTK2B switch pairs function as an ON/OFF switch (ON; activation of PTK2B-dependent angiogenesis pathway, OFF; inhibition of FGF2-dependent apoptosis pathway). Interestingly, some molecular switch pairs (for example, CHEK2-TP53) have been reported unique substitution of gene mutations in certain cancer (6). In gene-regulated molecular switches which consist of only transcriptional factors, nearly the same ON/OFF patterns among 4 medulloblastoma cell lines were observed (Fig. 2).

At least, a part of molecular switch pairs showed the dramatic ON/OFF expression patterns, indicating these switch pairs would be involved in the change of biological systems in tumorigenesis.

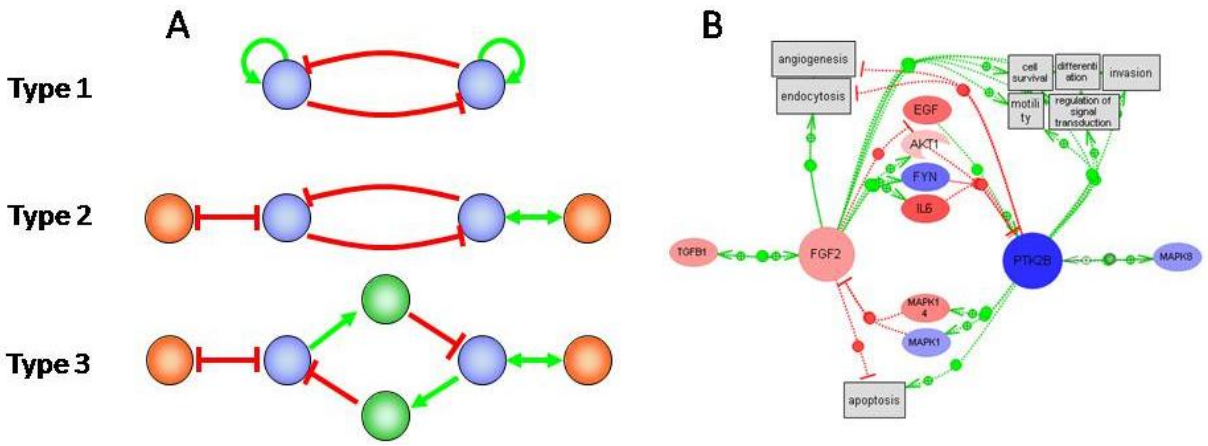

Fig. 1 **A**: molecular switch patterns. Green arrows represent positive (up-regulated) interaction and red lines represent negative (down-regulated). **B**: An example of molecular switch pairs (FGF2- PTK2B). Red nodes represent increased expression of mRNA of DAOY (medulloblastoma cell lines) compared with normal cerebellum. Blue nodes represent decreased expression.

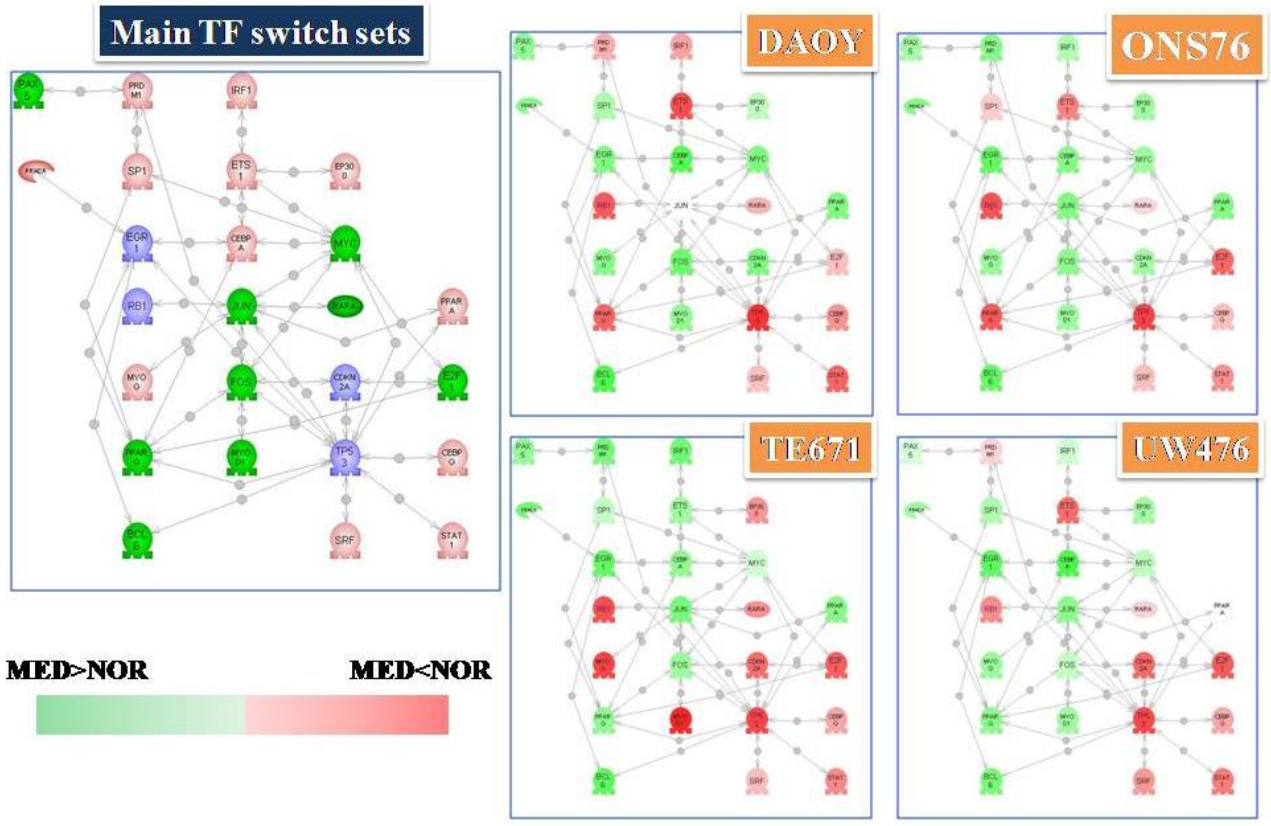

Fig. 2 The network of gene-regulated molecular switch pairs and their ON/OFF patterns in 4 medulloblastoma cell lines. MED; medulloblastoma, NOR; normal cerebellum

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