How Order of Mutations Affects Cancer Progression

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Clinical Observations

Two genetic mutations, JAK2 V617F (abbreviated as JAK2) and TET2, are commonly found in myeloproliferative neoplasm (MPN) patients.

Ortmann et al. observed that for MPN patients with JAK2 and TET2 mutations, which mutation appears first has effects on gene expression, cell population, and cancer progression.

Specifically, without TET2 mutation, JAK2 mutation can up-regulate certain genes (AURKB, MCM2, MCM4, MCM5, TK1).

With TET2 mutation, JAK2 mutation can down-regulate AURKB etc.

We build a quantitative model to explain this phenomenon.

Gene Regulatory Network

JAK2 V617 mutation

(a)

(d)

PRMT5 — (b) → E2F1 — (c) → { AURKB, MCM2, MCM4, MCM5, TK1 }
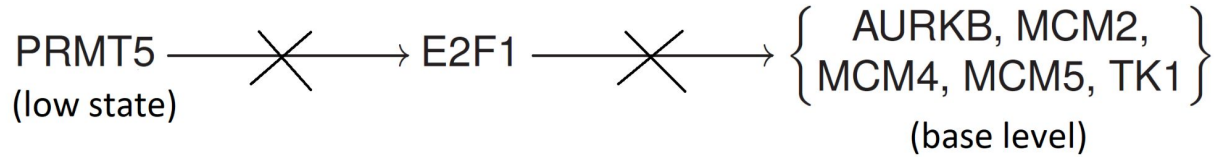
(e)

(e)
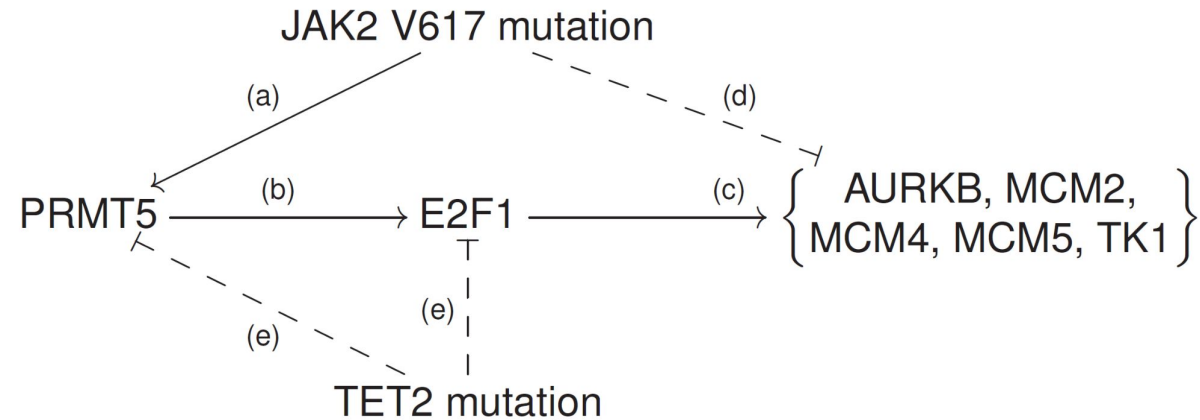
TET2 mutation

Regulations (a,b,c) are known.

Regulations (d,e) are hypothetical. One can verify them experimentally.

PRMT5 has two expression levels: low state and high state.

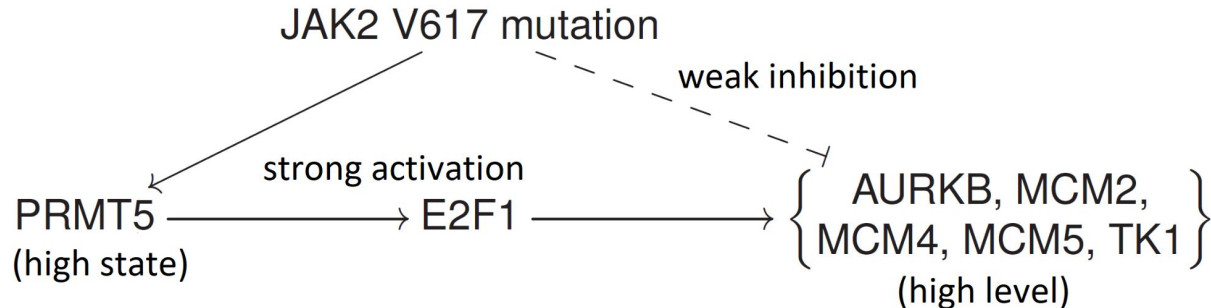If TET2 mutation is present, PRMT5 is locked to the low state, and cannot regulate AURKB etc.

If TET2 mutation is not present, JAK2 mutation can activate PRMT5 from the low state to the high state, and strongly promote AURKB etc.
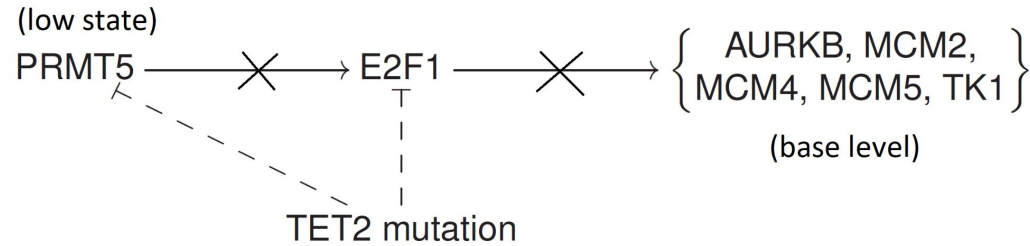
Without TET2 Mutation

PRMT5 ——————✕——————→ E2F1 ——————✕——————→ { AURKB, MCM2, MCM4, MCM5, TK1 }
(low state)   (base level)

JAK2 V617 mutation
                              weak inhibition
strong activation
PRMT5 ——————————→ E2F1 ——————————————→ { AURKB, MCM2, MCM4, MCM5, TK1 }
(high state)   (high level)

JAK2 up-regulates

AURKB etc.

With TET2 Mutation

(low state)

PRMT5 ──✗──→ E2F1 ──✗──→ { AURKB, MCM2, MCM4, MCM5, TK1 }

(base level)

TET2 mutation

JAK2 V617 mutation

weak inhibition

(low state)

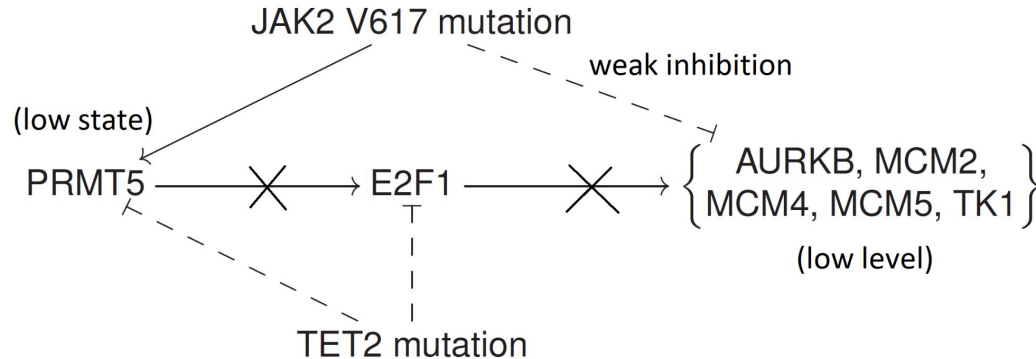PRMT5 ──✗──→ E2F1 ──✗──→ { AURKB, MCM2, MCM4, MCM5, TK1 }

(low level)

TET2 mutation

JAK2 down-regulates

AURKB etc.

Other Results

For cells with both JAK2 and TET2 mutations, the appearance order of mutations still affects gene expression.

The order of mutations also affects the composition of cell population with different mutations.

For patients with JAK2 appears before TET2, the age at diagnosis is much younger.

Come to the poster session for mathematical models that explain them all.