Baicalein Induces $p27^{kip}$ Degradation Through PI3K-Akt Pathway in Oral Cancer Cells

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Baicalein is a flavonoid known to have anti-inflammatory and anti-cancer effects. In a previous study, we reported that baicalein induced hypophosphorylation of Rb, causing G1 phase arrest through activation of AhR and down-regulation of cyclin D1 and CDK4 in oral cancer cells (HSC-3). In this study, we found that in baicalein-treated HSC-3, although Rb was hypophosphorylated, the expression of $p27^{kip}$, a CDK inhibitor was decreased to a level less than that in cells without baicalein treatment, which suggests that the reduction of $P27^{kip}$ may not be one of the causes of the hypophosphorylation of Rb. Using Western Blot to investigate how baicalein down-regulates $p27^{kip}$ expression, we found that baicalein treatment induced an increase in the amount of phosphorylated Akt (pAkt) at 12 and 24h. Such an increase caused an immediate corresponding reduction of the $p27^{kip}$. To confirm the association of Akt pathway with the $p27^{kip}$ degradation, we pretreated the cells with an Akt inhibitor, MK2206, and demonstrated that the blocking of phosphorylation of Akt reversed the expression of $p27^{kip}$ and reduced phosphorylated $p27^{kip}$ (Thr187) at 12 and 24h in the baicalein-treated cells. Knowing that PI3K is an upstream signal protein of Akt, we further pretreated the cells with a PI3K inhibitor, LY294002, and demonstrated that the level of pAkt was decreased, whereas the reduction of $p27^{kip}$ was slightly reversed and phosphorylated $p27^{kip}$ (Thr187) was decreased in the baicalein-treated cells. This indicates that, in baicalein-treated HSC-3, activation of PI3K induces phosphorylation of Akt and a subsequent signaling, which in turn increases phosphorylation of $p27^{kip}$ (Thr187), and thereby increases the degradation of $p27^{kip}$. Our data revealed that baicalein down-regulates $p27^{kip}$ through the PI3K-Akt pathway in oral cancer cells. Since down-regulation of $p27^{kip}$ is reportedly correlated with oral squamous cell carcinoma (OSCC) and its metastasis, with a poor prognosis for patients, our results suggest that baicalein‘s effect on the reduction of $p27^{kip}$ in the oral cancer cells may have a negative effect by inducing tumor cell migration and invasion-- thus countering baicalein’s positive effect of inhibiting tumor growth (via reduction of cyclinD1 and CDK4). Further studies are urgently needed to determine the exact impact of down-regulation of $p27^{kip}$ on baicalein-treated cancer cells.