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Letter to the Editor

Reply: Somatic mutations are present in all members of the AKT family in endometrial carcinoma

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Sir,

We appreciate the attention given by Drs Dutt, Salvesen, Greulich, Sellers, Beroukhim and Meyerson to our recent publication 'The oncogenic mutation in the pleckstrin homology domain of AKT1 in endometrial carcinomas' (Shoji *et al*, 2009). In this article, we report a 2% mutational frequency of *AKT1* (E17K) among 101 endometrial carcinomas. We also described that these two *AKT1* mutant tumours do not possess any mutations in *PIK3CA*, *PTEN* and *K-Ras*. Our report has proposed two issues to be clarified: (1) Are there any 'oncogenic' mutations in other AKT family members in endometrial carcinomas? (2) Are all the AKT family mutations mutually exclusive with other PI3 kinase-AKT-activating mutations?

Including the data in their earlier report, Dutt *et al* (2008) revealed mutations in *AKT2* and *AKT3*, as well as in *AKT1*. As for *AKT1* (E17K) mutations, their data and our data are compatible, showing that *AKT1* mutations were detected in 2% of the endometrioid subtype in endometrial cancer. Compared with the accumulative data in *AKT1* (E17K) mutations, mutations in *AKT2* and *AKT3* are not well characterised. Carpten *et al* (2007) and Kim *et al* (2008) reported no E17K mutations in *AKT2* and *AKT3* in breast, colorectal, gastric, hepatocellular, lung carcinomas and acute leukaemias. Davies *et al* (2008) first reported *AKT3* (E17K) mutations in melanoma at 1.5% frequency. Parsons *et al* (2005) found two mutations of *AKT2* (S302G and R371H) in 204 colorectal cancer samples, and Soung *et al* (2006) reported one missense mutation (A377V) and two possible splice-site mutations in intron 11 of *AKT2* in gastric and lung adenocarcinoma. However, the physiological role of *AKT2* mutations, including those (D399N, R368C and D32H) reported by Dutt *et al* (2008), has not been validated yet. In addition, the *AKT3* (E438D) mutation has not been reported in any type of tumours. It is important to clarify whether these rare AKT2/3 mutations cause an oncogenic effect in cancer.

We previously reported that *PIK3CA* mutations frequently coexist with mutations in *PTEN* and/or *KRAS*, and suggested that the *PIK3CA* mutation might require another upstream input to fully activate the PI3K kinase – AKT pathway (Oda *et al*, 2005, 2008). Their data of coexistent mutations in *AKT1* (E17K) and *KRAS* (G13D) suggest that the *KRAS* mutation alone is insufficient for a full activation of the PI3 kinase – AKT pathway. Their data are not inconsistent with the hypothesis that the *AKT1* (E17K) mutation and the *PIK3CA* mutation are mutually exclusive. The coexistent mutations of *AKT3* and *PIK3CA* in one sample suggest that some types of *AKT* mutations (non-E17K) might coexist with *PIK3CA* mutations to enhance the activation of the PI3 kinase – AKT pathway. Further analyses are necessary to clarify the frequency of coexistent mutations in *AKT1* (E17K), *AKT2/3* and other mutations.

Their current data and our data suggest that the PI3 kinase – AKT pathway is prevalently activated in endometrial cancer through various genetic alterations and their combinations. Further analyses in *AKT*, *PIK3CA* and other PI3 kinase-AKT-related genes would be helpful to comprehensively understand the mechanism of activation in this pathway and to use PI3K-targeted therapies in various types of cancer.

We thank Dr Dutt and colleagues for their recognition of our work.

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